A STUDY OF CORRELATION OF DISEASE SEVERITY BY CLINICAL ASSESSMENT, RADIOLOGICAL ASSESSMENT AND IgG RHEUMATOID FACTOR IN PATIENTS WITH RHEUMATOID ARTHRITIS

A Dissertation Submitted to

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI

In Partial Fulfillment of the Regulations

for the Award of the Degree of

M.D. (GENERAL MEDICINE) - BRANCH – I

GOVERNMENT KILPAUK MEDICAL COLLEGE

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BONAFIDE CERTIFICATE

This is to certify that **"A study of correlation of disease severity by clinical assessment, radiological assessment and IgG Rheumatoid Factor in patients with rheumatoid arthritis"** is a bonafide work performed by**Dr.Madhav.V.**, post graduate student, Department of Internal Medicine, Kilpauk Medical College, Chennai-10, under the guidance and supervisionof Prof. Dr.N. GUNASEKARAN, M.D., DTCD, Head of the Department of Medicine, Kilpauk Medical Collegein fulfilment of regulations of the Tamil Nadu Dr. M.G.R Medical university for the award of M.D. Degree Branch I (General Medicine) during the academic period from May 2011 to April 2014.

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DECLARATION

I solemnly declare that this dissertation **"A study of correlation of disease severity by clinical assessment, radiological assessment and IgG Rheumatoid Factor in patients with rheumatoid arthritis"** was prepared by me at Government Kilpauk Medical College and Hospital, Chennai, under the guidance and supervision of **Dr. G.Balan M.D.**, Professor and Head of the Department of Internal Medicine, Government Kilpauk Medical College and Hospital, Chennai.

This dissertation is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfilment of the University regulations for the award of the degree of **M.D. Branch I (General Medicine)**.

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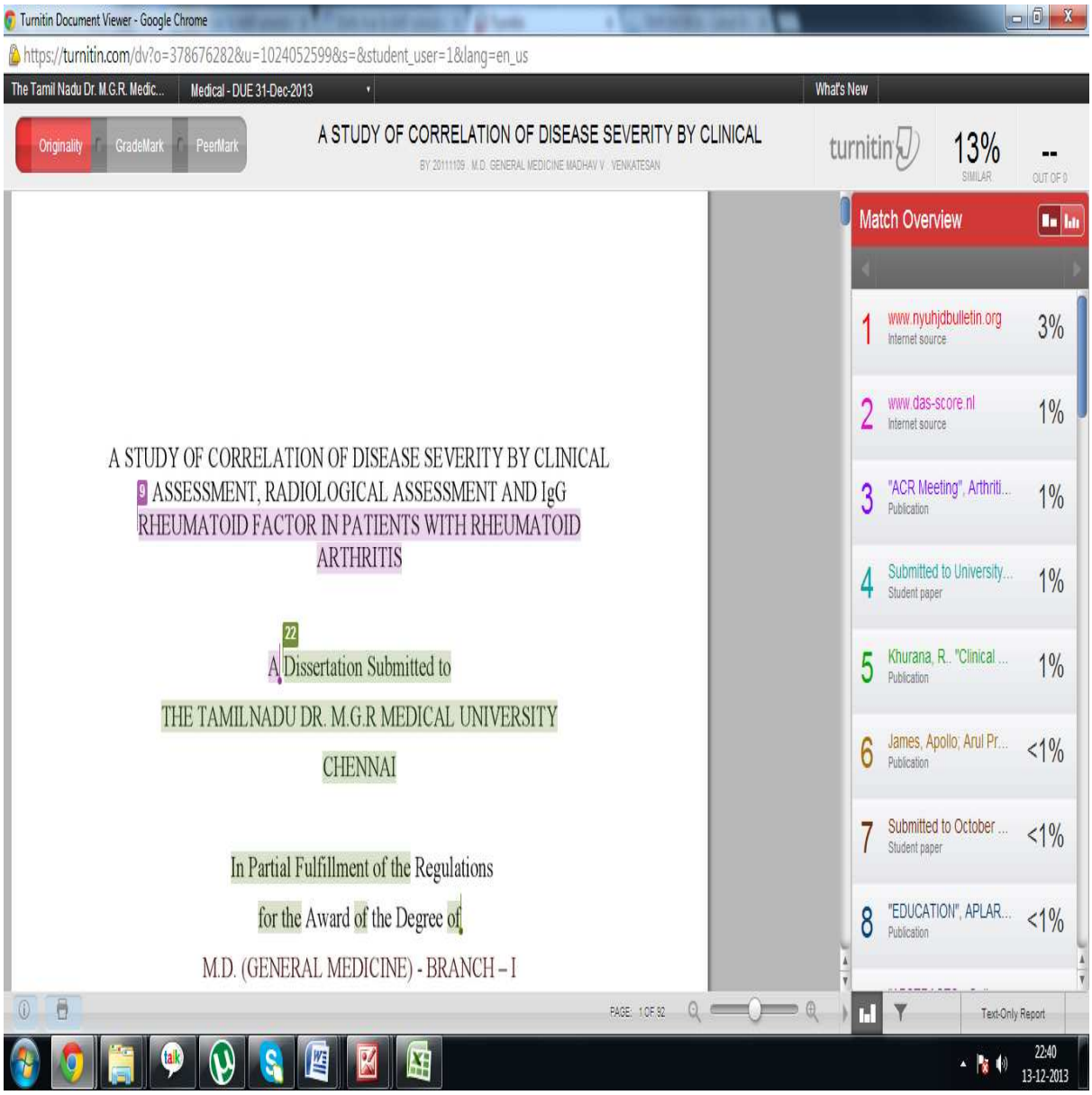
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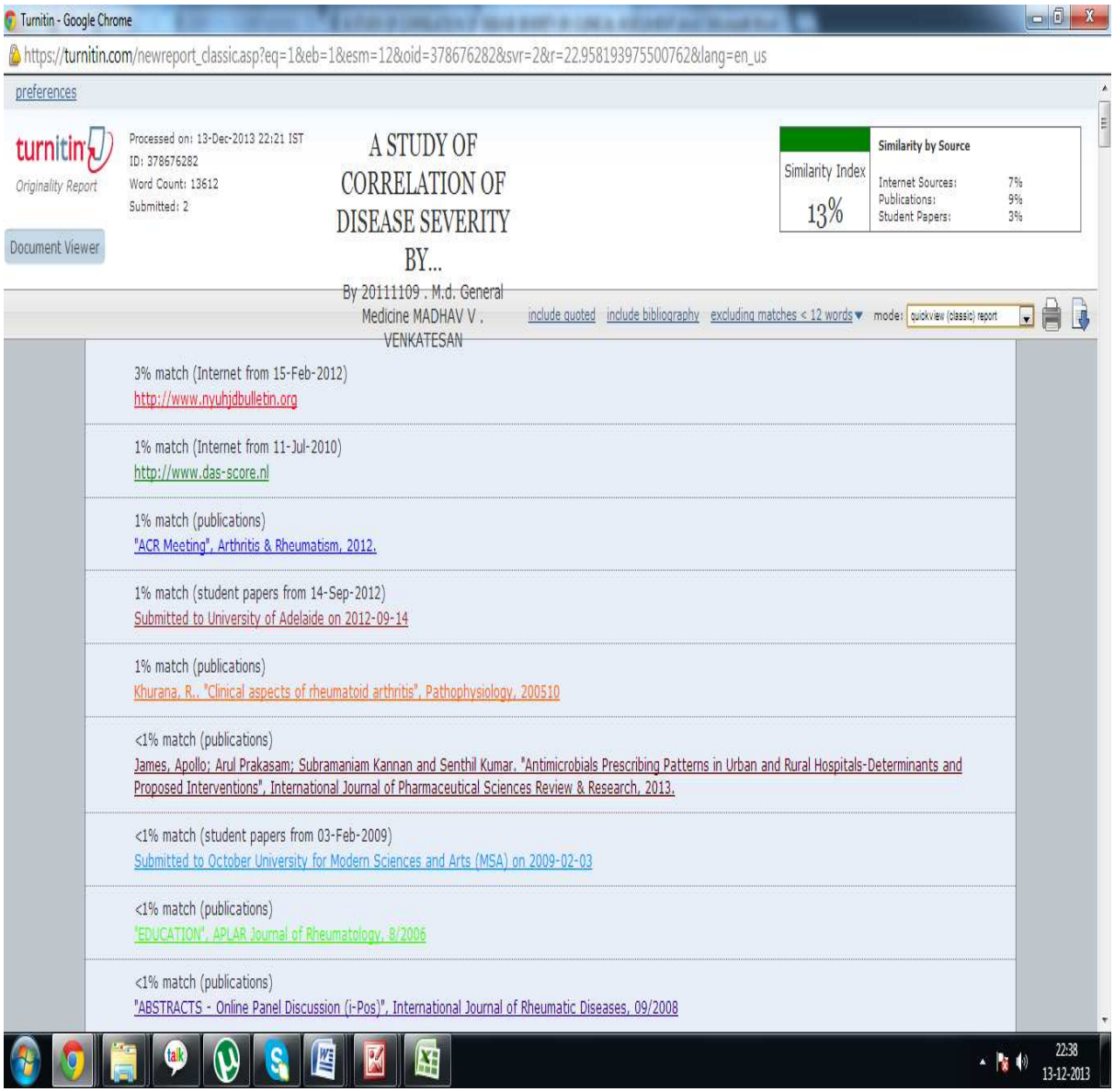
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CONTENTS **PAGE No.**

1. Introduction 01

2. Aim of study 03

3. Review of literature 04

4. Materials and methods 48

5. Observations and analysis 59

6. Discussion 84

7. Conclusions 88

8. Limitations and recommendations. 89

APPENDIX

Bibliography

Abbreviations

Questionnaire

Master chart

Ethical committee approval certificate

A STUDY OF CORRELATION OF DISEASE SEVERITY BY CLINICAL ASSESSMENT, RADIOLOGICAL ASSESSMENT AND IgG RHEUMATOID FACTOR IN PATIENTS WITH RHEUMATOID ARTHRITIS

ABSTRACT

Background: Rheumatoid arthritis is a chronic, autoimmune disease of inflammatory nature which generally affects the joints and multiple organs and is often debilitating in nature. Though various studies have been done regarding the disease, a lot about the disease still remains unknown.

Objective: The main aim of the study is to determine the correlation between the disease activity scale (DAS28) and radiological severity scale (Van der Heijde modification of Sharp score) in patients who present with rheumatoid arthritis. This study also determines the efficacy of IgG RF in determining radiological progression in the same patients.

Materials and methods: The patients were selected using the ACR/EULAR criteria for RA. The DAS 28 and modified Sharp's Scale were obtained with consent and blood drawn and checked for IgG RF positivity along with other required investigations and the results studied using the statistics described in the study.

Results: Though patients with increased DAS 28 scores tended to have higher Sharp's scores there was no significant correlation between the two.($p=0.069$)

There was however a definite positive correlation between the IgG RF and modified Sharp's score.($p < 0.01$)

Conclusions: Though both DAS28 and Sharp score both help to determine the severity of the disease, they detect two different aspects of the same disease and are hence not changeable. Sharp score and other radiological scale do not determine of the severity of the disease but detect bony changes that predict long term morbidity. Though IgM RF and anti CCP are most commonly used in RA, IgG RF predicts radiological changes like bony erosions and joint space narrowing and can hence be used to predict long term changes.

Keywords: rheumatoid, arthritis, DAS28, Sharp , IgG RF, severity

1. INTRODUCTION:

Rheumatoid arthritis is a chronic, autoimmune disease of inflammatory nature which generally affects the joints and multiple organs and is often debilitating in nature. Though various mechanisms of pathogenesis have been discussed the exact cause is not yet known. The prevalence of the disease is about 0.8%(0.5% - 1%)[1] Over the years, various major discoveries have lead us to bring about earlier diagnosis of RA and manage those patients better.

The advent of DMARDs and later biologics has changed the way of treatment of RA.[2] With various modes of treatment available it has now become essential for us to estimate the extent and the severity of the disease initially during presentation to plan our management. It is also very important to have proper universal scales to determine effectiveness of the treatment given and estimate prognosis.[3]

There are various ways to determine the severity of the disease. In clinical practice physicians tend to check the severity of the disease as well as detect prognosis and response to drugs using certain scoring systems. The commonly used clinical severity scales for both practise and clinical trials tend to use factors like swollen joints, tender joints, markers of inflammation and various questionnaires giving what the patient feels about the disability.[4,5] These scores generally give a very good idea about the acute pathological process and immediate and short term response to drugs. However a major part

of the pathogenesis of RA is the long term complications especially on the joints which lead to permanent and debilitating disability. Hence radiological investigations like radiographs have always been a major part of the management of the disease.[6] There is however no clear indication about how the various clinical severity scores and radiograph scores tend to correlate. Some literature states that clinical disability as measured by the clinical scales is an acute pathology which is differs from the chronic pathology which causes radiological changes like erosions.[7,8] There is another view which states that there is a proper correlation between the two scoring systems with regard to patient's disease. However further studies are needed.

Also the role of positivity of antibodies specific to RA and their correlation with the severity indices is also a subject of debate with some studies showing that antibodies like IgG RF and anti CCP tend to correlate well with radiological progression of the disease.[9,10]

This study aims to correlate the commonly used clinical severity scale (DAS28) and commonly used radiological scale (Van der Heijde modification of Sharp score) to determine if there is a positive correlation between the two. It also hopes to determine the efficacy of IgG RF in determining radiological progressions in RA.

2. AIM OF THE STUDY

1. To study the correlation between the disease activity scale (DAS28) and the commonly used radiological severity scale (Van der Heijde modification of Sharp score) in patients who present with rheumatoid arthritis in Govt. Kilpauk Medical College, Chennai.
2. To determine the efficacy of IgG RF in determining radiological progression in the same patients.

3. REVIEW OF LITERATURE

3.1 HISTORICAL REVIEW:

Rheumatoid arthritis and other associated arthritis have been documented in medical literature since 1500 B.C. The first mention of the disease from ancient scrolls comes around 1500 B.C. when the Ebers Papyrus describes a condition that is similar to rheumatoid arthritis. In his book "Treatise on Rheumatism and Rheumatoid Arthritis", Archibald Garrod refers to bones in ancient skeletal findings from around the world, which includes the ruins of Pompei , a graveyard in Pomerania (Poland-Germany border), remains of a Norse Viking and from ancient Egypt.[11] In India , "Charak Samhita" (written as early as 500 BC) describes patients with pain and swelling of joints along with loss of mobility and function.[12]Descriptions about Rheumatoid arthritis were also given by Hippocrates in 460 B.C. and Scribonius Largus in Roman literature around 100 A.D. In modern medicine, Augustin Jacob Landre-Beauvais mentioned patients who suffered from a new arthritis in 1800 and termed it Goutte Asthenique Primitive (Primary Asthenic Gout).[13] In 1859, Alfred Garrod differentiated RA from gout in his book "Treatise on Nature of Gout and Rheumatic Gout"[14] and later in 1890 coined the name "Rheumatoid Arthritis".[15] The term Rheumatoid arthritis was then accepted by the British Nomenclature in 1922 and by the United States Nomenclature in 1941.[16]

3.2 DEFINITION:

Rheumatoid arthritis is a chronic autoimmune disease of unknown etiology with multisystem involvement. Although it is mainly seen as a disease involving the joints it is evident that there is abnormal systemic immune response and this results in extra-articular manifestations. The most characteristic feature of Rheumatoid arthritis remains the persistent inflammatory synovitis involving peripheral joints usually in a symmetrical combination. This results in the damage of the cartilages, bony erosions and changes in the integrity of the joints which is the hallmark of the disease.

3.3 EPIDEMIOLOGICAL REVIEW:

Rheumatoid arthritis is seen all over the world, except in a few population like the Chinese, Pima Indians of North America, Caribbean blacks and rural Sub-Saharan Africans where the incidence is very low.[17] The various studies about the epidemiology of RA gives a population prevalence of 0.5%-1% of the general population which increases with age and reaches a maximum at the ages of 35 to 50 years.[18] There are gender differences with females affected 3 times more than men.[18]The prevalence of Rheumatoid Arthritis in India is found to be 0.75% which is similar to the disease's prevalence seen in developed countries.[19]

3.4 ETIOLOGY:

Though the precise cause of RA is still not known, many studies show that environment and genetic factors play an important role in the pathogenesis.

3.4.1 GENETIC FACTORS

Among the various etiological factors, genetic factors account for about 50% of the risk of developing rheumatoid arthritis.[20]The importance of genetics in RA is clearly seen from the fact that concordance rates in monozygotic twins is 12% to 15% when one twin is affected, compared to 4% for dizygotic twins and 1% for the general population.[21] Siblings of patients suffering from RA have a two to four fold increased chance of developing RA as compared to unrelated population.[17,22]

The most consistent and probably the most influential genetic risk factor is the Class II MHC haplotype of an individual. Many other genes are also involved and only a percentage of them have been presumed to have been studied.

HLA DR4B is associated with the maximum susceptibility to RA. Others include HLA DR1B and HLA DR14.[23] It had been found that in some population about 96% of patients with RA have the susceptible HLA-DR locus. Some HLA genes like DRB*1301 are associated with less susceptibility to the disease.[24]

Old Nomenclature (HLA-DRB1 Alleles)	Current Nomenclature	Association with Rheumatoid Arthritis
HLA-DR1	0101	+
HLA-DR4 Dw4	0401	+
HLA-DR4 Dw14	0404/0408	+
HLA-DRw14 Dw16	1402	+
HLA-DR4 Dw10	0402	–
HLA-DR2	1501, 1502, 1601, 1602	–
HLA-DR3	0301, 0302	–
HLA-DR5	1101-1104, 1201, 1202	–
HLA-DR7	0701, 0702	–
HLA-DRw8	0801, 0803	–
HLA-DR9	0901	–
HLA-DRw10	1001	–
HLA-DRw13	1301-1304	1301 associated with protection
HLA-DRw14 Dw9	1401	–

Non HLA genes[25]:

IL-1 gene cluster

TNF receptors I and II

CTLA-4

Fc γ-receptor II/III loci

SLC22A4

SLC22A5

Additional Polymorphisms[17]

1. Cytokine polymorphism (TNF)[26]

2. PADI4[27]

3. PTPN22[28]

4. STAT4

5. IL2/21

6. TRAF1-C5

Having a combination of susceptible genes tend to increase the risk as these genes were found to interact with each other.

3.4.2 ENVIRONMENTAL FACTORS

1. Smoking is considered as the best defined environmental risk factor to cause seropositive Rheumatoid arthritis.[29] Though its mechanism is not certain it could possibly involve the activation of PADI and innate immunity in the lungs.[17]

2. Infectious agents: Though there are no conclusive evidences, it has been postulated through various studies that infectious agents can trigger disease by activation of the innate immunity or by molecular mimicry. These include Mycoplasma, Parvovirus B19, Retrovirus, Mycobacterium and EBV.[17] Rheumatoid arthritis also appears to be related to periodontal disease due to Porphyromonas gingivalis which expresses PADI4.[30] The following table

gives the commonly discussed infections and their potential mechanism of action

Infectious Agent	Potential Pathogenic Mechanisms
Mycoplasma	Direct synovial infection; superantigens
Parvovirus B19	Direct synovial infection
Retroviruses	Direct synovial infection
Enteric bacteria	Molecular mimicry (QKRAA, e.g., in bacterial heat shock proteins)
Mycobacterium	Molecular mimicry (proteoglycans, QKRAA), immunostimulatory DNA (Toll-like receptor 9 activation)
Epstein-Barr virus	Molecular mimicry (QKRAA in gp110)
Bacterial cell walls	Toll-like receptor 2 activation

3. Exposure to silica seen in granite workers and fish industry workers seem to confer increased risk for RA.

4. Selenium and copper deficiency can increase risk of RA possibly due to modulation of immunity.[31]

5. Some factors like consumption of alcohol, fish oil, olive oil and Vitamin C have been postulated with decreasing risk of developing RA.

6. Usage of oral contraceptive pills is said to reduce the incidence of rheumatoid arthritis.

3.4.3 HOST FACTORS:

There is a clear gender predisposition towards females in rheumatoid arthritis as already explained in the epidemiology. It is postulated that sex hormones play a role in the pathogenesis of RA, evidenced by the increased

presence in females. Pregnancy tends to reduce the intensity of the disease and postpartum flares tend to occur. It is now postulated that hyperprolactinemia might be a risk factor for RA.[32]

3.5 PATHOGENESIS

It is believed that the starting of the pathogenesis of rheumatoid arthritis begins years before the symptoms of the disease come to the fore. It is believed that the disease is triggered by the repeated exposures of a genetically vulnerable host to an arthritogenic antigen. There is a continuous autoimmune reaction leading to CD4 helper T cells and B cells activation. These result in local release of inflammatory mediators and cytokines which ultimately lead to destruction of the joints.

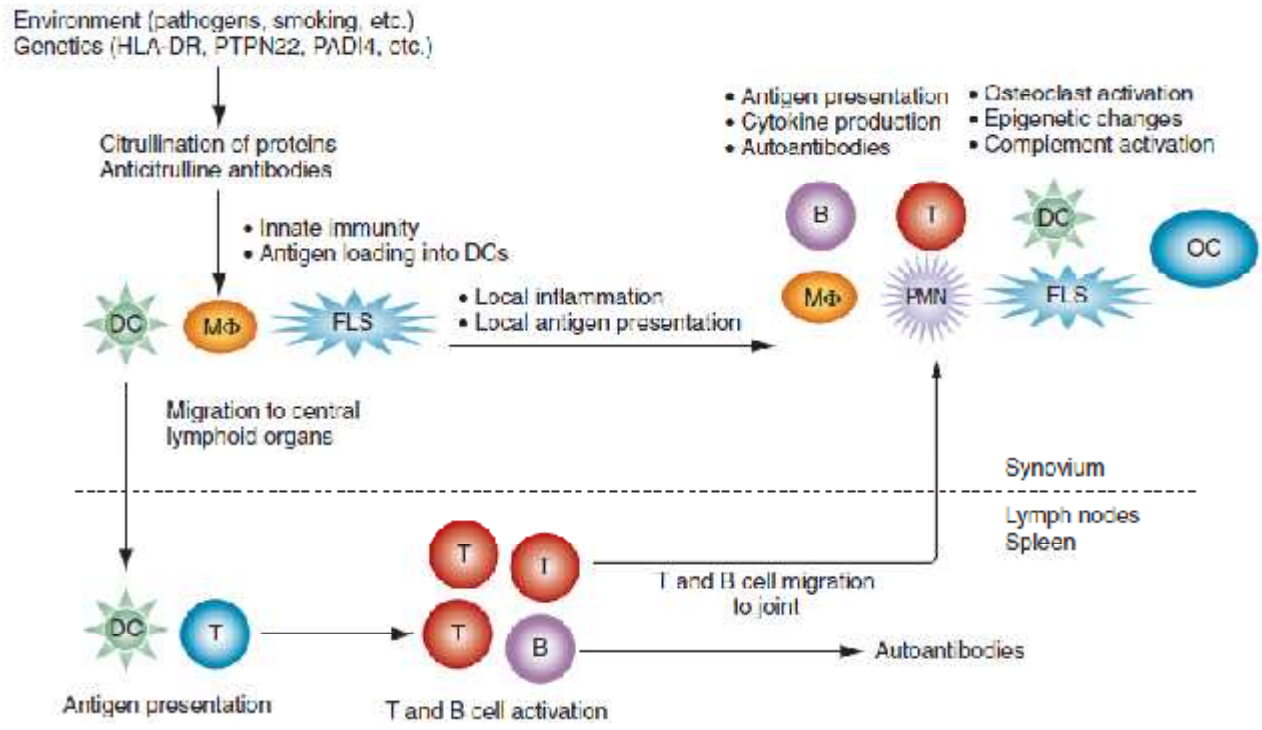
In genetically susceptible individuals (patients with genes that break tolerance and results in auto reactivity), host factors and environmental factors (discussed above) result in repeated activation of innate immunity. The environmental factors are important as they lead to post transcriptional modifications of proteins, most important among these being the citrullination of arginine residues either in the synovium or in the mucosal surfaces. These can occur in normal individuals also, but in genetically susceptible individuals where tolerance is broken, this can lead to development of antibodies against these modified proteins notably Rheumatoid Factor antibodies (RF) and anti citrullinated antibodies (anti- CCP).

The synovium is attacked by activation of the synovial innate immunity. The antigen presentation done by the dendritic cells is done both in the synovial germinal centres and also more commonly after the dendritic cells travel through the lymphatics and reach the central lymphoid system. Naive T cells are activated and they stimulate the B cells to produce pathogenic antibodies or migrate to the synovium and produce inflammatory cytokines like IL-17. This results in repeated episodes of inflammation which then progresses to a destructive phase having both antigen dependent and antigen independent mechanisms which are mediated by mesenchymal components like synoviocytes and fibroblasts. As the disease progresses many cell types (especially fibroblasts) acting via the nuclear factor κβ (NFκβ) activate the NFκβ ligand (RANK/RANKL) system which activates osteoclasts. The osteoclasts cause bone erosions while the proteolytic enzymes released by the the synoviocytes and synovial fluid neutrophils cause cartilage dissolution.

The primary inflammation site in rheumatoid arthritis is the synovium. Synovitis occurs when the synovial compartment is infiltrated by leucocytes which migrate to the synovium due to activation of endothelium of synovial microvessels, resulting in expression of adhesion molecules and release of chemokines. Neoangiogenesis caused by the cytokines and local hypoxic conditions along with insufficient lymphangiogenesis (which reduces cellular egress), are features of early synovitis. Along with these microvascular injuries,

the other earliest lesion in rheumatoid synovitis appears to be the increase in synovial lining cells. The increase in synovial lining cells can be quite high. In normal joints it is only 1-2 cell layer deep, while in joints inflicted with RA it can be 4-10 cell layers deep.[17] There are two different types of cells in the lining. Type A synoviocytes resemble a macrophage while Type B synoviocytes are fibroblast like cell. Though there is an increase in number in both the cells, there is much more increase in Type A cells.

PATHOGENESIS IN RHEUMATOID ARTHRITIS



Adaptive immunity pathways are the epicentre of the early pathogenesis of RA. In microscopic examination CD4 memory cells are aggregated around

the post capillary venules, B cells are located within reactive lymphoid cells, with plasma cells and macrophages outside the centre which is consistent with T cell dependent B lymphocyte activation. B cell activation by CD4+ Helper T cells result in antibodies and immunoglobulin formation within the synovium and results in immune complex formation. These antibody complexes as well as different antibodies contribute to the synovitis. Moreover the synovial fibroblasts in RA release numerous enzymes like cathepsins and collagenases which degrade the various components of articular matrix. Besides these various enzymes and cells, T lymphocytes, fibroblasts, myeloid cells and endothelial cells of the synovium also release various cytokines and chemokines. These also play an important role in the pathogenesis of rheumatoid arthritis.

In the synovium of patients with RA, CD4+ T cells differentiate more into T_H1 like effector cells that produce the proinflammatory cytokines like IFNγ rather than differentiation into T_H2 like effector cells that are capable of producing anti-inflammatory cytokines like IL-4. Therefore there is a continuous secretion of pro-inflammatory cytokine IFNγ without anti-inflammatory cytokine IL-4 and as a result of this imbalance macrophages which secrete other pro-inflammatory cytokines likes IL-1 and TNF are activated. These macrophages also increase the expression of pro-inflammatory molecules. T lymphocytes express CD154 and also release a variety of

cytokines which promote B cell proliferation and differentiation into antibody forming cells. The production of RF , anti-CCP and other immunoglobulins which occur as a result of this leads to formation of immune complexes which result in activation of complements and exacerbation of inflammation by formation of C3a ,C5a and other anaphylatoxins.[33]

Beside this chronic inflammation which occurs in the synovial tissue, a simultaneous acute inflammatory process also occurs in the synovial fluid. Antibodies are produced locally in response to tissue compartments and immune complexes and these activate complements and also generate chemotactic factors and anaphylatoxins. Along with these, leukotriene B4 and products of complement activation also attract neutrophils. The net result of all these is the increased migration of polymorphonuclear leucocytes to the synovium. These polymorphonuclear leucocytes ingest immune complexes and produce reactive oxygen metabolites and other proinflammatory mediators. The production of large amounts of lipoxygenase and cyclo-oxygenase products by the cells in the synovium and its fluid further worsens the inflammation in these patients.[34]

The pathological tissue component in RA is the pannus. Pannus is a highly vascular granulation tissue which is composed of small blood vessels, proliferating fibroblasts and mononuclear cells. The synovial fluid contains many enzymes that can degrade the cartilages, especially in the juxta-position of

the pannus. Pannus can produce a large number of enzymes like stromelysin and collagenase which can lead to tissue damage. The macrophages and fibroblasts also produce PGE_2 which can also contribute to bone mineralisation. The final common pathway that leads to bone mineralisation most likely involves the activation of osteoclasts that are present in large numbers at the site. The major agents causing the systemic manifestations of RA, which includes fever, malaise and increased acute phase reactants, are IL-1 and TNF. The immune complexes which escape the synovium can get deposited in the blood vessels causing vasculitic changes.

3.6 CLINICAL FEATURES

There are 3 patterns of onset of the clinical picture of rheumatoid arthritis.

Insidious onset – 55 % to 65% of patients with RA present with a slow onset disease which progresses over weeks to months.[35] They can present with either systemic features or joint involvements. Non specific symptoms like fatigue, malaise, diffuse musculoskeletal pain and swollen joints can be the initial presentation with specific joints involved later in the course of the disease. At the time of initial presentation asymmetric involvement of joints are common, but unlike other arthritis, RA quickly tends to involve symmetrical joints.[8] Symptoms tend to persist in the initially affected joints as they progress to other joint and hence are not truly migratory.

Acute onset – 8% to 15% of patients have an acute onset of presentation with symptoms often less symmetrical than the insidious onset of presentation. The differential diagnosis for this type of presentation includes sepsis and vasculitis.

Intermediate onset – In 15% to 20% of people symptoms develop over days to weeks. Systemic symptoms are more markedly seen in these patients when compared to those who have an insidious onset.

Morning stiffness is an important and characteristic sign of inflammatory arthritis that is frequently seen in patients with rheumatoid arthritis. It is caused by accumulation of oedema fluid in the inflamed tissues as the patient is sleeping. Once the patient wakes up and starts moving his joints, the excess oedema is drained by the venules and lymphatics which open up with the articulation of joints. Morning stiffness greater than 30 to 45 minutes is characteristic of inflammatory arthritis and can sometimes precede pain.

3.6.1 Joint involvement:

The joints frequently involved first in rheumatoid arthritis includes the metacarpophalangeal (MCP) joints, the proximal interphalangeal(PIP) joints and the wrists in the upper limbs along with the metatarsophalangeal joints in the lower limbs.[36] Larger joints usually become symptomatic after the small joints. In larger joints the synovitis appears to remain asymptomatic for a longer

period of time and active synovitis is seen in biopsy specimens of quiescent large joints.[37]

Joint Involvement	% Patients (Mean)	% Patients (Range)
MCP, PIP	91	74-100
Wrists	78	54-82
Knees	64	41-94
Shoulders	65	33-75
Ankles	50	10-67
Feet	43	15-73
Elbows	38	13-60
Hips	17	0-40
Temporomandibular	8	0-28
Spine	4	0-11
Sternoclavicular	2	0-6
Peri-articular sites	27	20-29

INVOLVEMENT OF SPECIFIC JOINTS:

Hand and wrist:

They are considered together as they share common disabilities for the patient and form a functional unit. One of the earliest signs of RA is the swelling on the dorsal side of the wrist especially involving the tendon sheaths of extensor carpi ulnaris and extensor digitorum communis. Sometimes cystic structures on the dorsal aspect of the wrist and hands resembling a ganglion are early features of RA. As synovial proliferation increases within the joint, the pressure which is built up inside the synovium along with the enzymes begin to destroy tendons, ligaments and bones distal to the ulnar head. The ulnar collateral ligament is stretched and finally ruptures causing the ulna to cause a

dorsal prominence which can be depressed (piano key styloid). On the volar side, synovial protrusion cysts are formed and can be palpated. The hyperplastic synovium can compress the median nerve and cause carpal tunnel syndrome. One of the characteristic deformities seen in the fingers is the swan neck deformity which is formed by the flexion of the metacarpophalangeal (MCP) joint and the distal interphalangeal joint (DIP) along with hyperextension of the proximal phalangeal joint (PIP). It starts with the shortening of the interosseous muscles which causes tension on the dorsal tendon sheath. This leads to the hyperextension of PIP causing the characteristic deformity.[38] Sometimes during the course of chronic RA, the extensor hood around the PIP may get avulsed due to chronic inflammation causing a boutonniere deformity. In the thumb, besides the boutonniere deformity, inflammation of the carpometacarpal joint can cause volar subluxation when contracture of the adductor hallucis develops. Another common presentation seen in the hand is tenosynovitis of the fingers like de Quervain's tenosynovitis. Sometimes the rheumatoid nodules in the tendon tend to lock the fingers in a painful fixed flexion position or cause 'trigger' fingers. As disease progress the there is severe resorption of bone. This resorption begins in the articular cartilage and extends along the diaphysis of the phalanges causing the digits to be shortened. As a result of these changes the digits are shortened, skin folds are present excessively. As the disease progresses the phalanges can be telescoped into each other and often pulled out into long extension without pain. If the patient is not properly treated the end

result of all these changes is bony ankylosis. Bony ankylosis is usually found in joints that have been immobilised either by inflammation, pain or treatment. Grip strength is a very sensitive indicator of hand involvement as it simultaneously tests multiple joints of the hands.[17] Muscular contraction in the grip strength test causes tightening of the ligaments around the joints, compressing an already inflamed synovium. The result is weakness along with pain due to the reflex contraction of muscles due to pain.

Disease of the wrist usually goes along with disease of the fingers as they are a combined unit. Weakness of the extensor carpi ulnaris causes radial deviation in the wrist. In response to this there is an ulnar deviation of the fingers to keep the tendons of the phalanges in a normal straight line to the radius. This causes the characteristic "zigzag" deformity which is seen in RA.

Elbow:

It is involved in 20% to 65% of the patients. One of the earliest finding seen in patients is loss of full extension. Fortunately this can be partially compensated by the actions of the shoulder joint and wrist joint. As the elbow is a stable hinge joint, it is rarely involved with pain but if the lateral stability is lost then the disability can be severe.

Shoulder joint:

In the shoulder, RA affects the synovium, distal third of the clavicle, rotator cuff, various bursa and also many muscles surrounding the joint. The involvement of the rotator cuff is a major cause of morbidity. Weakness of the

cuff leads to superior subluxation. Aging and previous injury tends to increase the chances of tears of the rotator cuffs. This occurs due to increased erosion by the proliferating synovitis. Radiographic examinations of the shoulder generally show erosions and superior subluxation. Sometimes there might be associated chronic subacromial bursitis which is not generally associated with pain or loss of motion. There tends to be synovial proliferation within the subdeltoid bursa which can explain the resorption seen on the under surface of the distal clavicle. Very rarely, there is rupture of the shoulder joint which presents with symptoms resembling obstruction of venous drainage from arm.

Temporomandibular Joint:

This joint is commonly involved in RA. Studies show that 55% of RA patients have jaw symptoms at one time during the course of their disease. Radiographic studies reveal that there are structural alterations in 78% of the joints examined.[35] An overbite or an erosion can develop as the mandibular condyle along with the corresponding surface of the temporal bone, the eminentia articularis, is eroded. Sometimes patients have an acute pain and difficulty in closing the mouth which requires intra-articular glucocorticoid therapy to reduce the acute inflammatory process. As temporomandibular joint abnormalities are also commonly seen in non-rheumatoid population it is essential to differentiate the two. CT scan and MRI show erosions and cysts in the mandibular condyle which is generally specific for RA. However many

studies have shown that there is no correlation between the CT finding and clinical presentation of temporomandibular joints in patients with RA.[39]

Cricoarytenoid Joints:

Careful histories in patients with RA may reveal hoarseness in about 30% of rheumatoid patients and it is believed more patients have asymptomatic cricoarythenoid arthritis. Normally it is not crippling but in some patients it can become inflamed and immobilised and cause inspiratory stridor. Various studies show that there is a better correlation to mucosal and functional abnormalities like rheumatoid nodules seen in indirect laryngoscopy to symptoms of difficult inspiration rather than CT detected laryngeal abnormalities and hence indirect laryngoscopy is indicated in symptomatic patients.[40]

Sternoclavicular and Manubriosternal Joints:

Sternoclavicular and manubriosternal joints are frequently involved in RA. However as they are relatively immobile they are generally asymptomatic. Rarely patients give history of pain in the sternoclavicular joints while lying on specific sides. It is important to consider superimposed sepsis when symptoms do occur.

Cervical Spine :

Unlike other joints, the joints of the cervical spine frequently manifest osteochondral destruction. Though significant pain is frequently reported, in the absence of muscle spasm passive range of motion is frequently normal. The extension of the inflammatory process from the neurocentral joints into the

discovertebral area along with the chronic cervical instability due to apophyseal joint destruction lead to microfractures of the vertebral end plates, degeneration of disc cartilages and disc herniation. Among the bones in the cervical spine, there are special characteristics associated with the atlas and the atlantoaxial joint.

• The atlas can move anteriorly on its axis. This is due to the laxity of the ligaments caused by the formation of proliferative synovial tissue in synovial bursae and by erosion or fracture of the odontoid process. The atlas can also move posteriorly on the axis. This can occur if the odontoid peg is fractured from the axis or if it is destroyed. The atlas can also sublux vertically in relation to the axis. This occurs only very rarely. This results due to destruction of either the lateral atlantoaxial joints or the bone around the foramen magnum. The most common symptom which occurs in cervical subluxation is that of pain radiating up to the occiput. Other clinical presentations include slowly developing spastic quadriparesis with sensory loss in the hands and transient episodes of medullary dysfunction which can present as paresthesias in the shoulders and arms during movement of the head. Physical findings which are suggestive of atlantoaxial subluxation are loss of occipitocervical lordosis, resistance to passive spine motion along with abnormal protrusion of the axial arch which can be felt by our finger along the posterior pharyngeal wall.

Symptoms of spinal cord compression for which we should consider intervention are syncope, altered consciousness, loss of sphincter control,

dysphagia, convulsions, vertigo, hemiplegia, dysarthria, nystagmus, and peripheral paresthesias. Studies show that the progression of peripheral joint erosions in patients with RA parallels that of cervical spine .The two coincide in both severity and timing.

Thoracic, Lumbar, and Sacral Spine :

These portions of the spine are generally spared in RA. Exceptions include the apophyseal joints where rarely synovial cysts seen at the joint can impinge like an epidural mass on the spinal cord which causes pain, neurologic deficits or both.

Hips:

The hip is more frequently involved in juvenile RA than in adult onset RA. Symptoms of hip synovitis include pain in the lower buttocks or in the groin. Sometimes patients have trochanteric bursitis which presents as pain on the lateral aspect of the hip. About 50% of patients with well-established RA have radiological evidence of hip disease. In RA the symmetrical thinning of the cartilage lead to axial migration. Rarely there is collapse and resorption of the femoral head, resulting in the remodelling of the acetabulum which is pushed medially causing protrusio acetabuli.[41] Loss of internal rotation seen by physical examination correlates well with X rays and MRI. Similar to other weight-bearing joints, the femoral head can develop few cystic lesions that tend to communicate with the joint space.

Knees:

Synovial inflammation and its effects in the knees can be easily picked up by physical examination. As early as 1 week after the onset of symptoms noticeable quadriceps atrophy is present and this leads to the application of greater force through the patella to the femoral surface. Another early manifestation of knee disease seen in patients with RA is loss of full extension which is initially a functional loss that later tends to become a fixed flexion contracture unless early corrective measures are undertaken.

Flexion of a knee with a large effusion (secondary to synovial inflammation) tends to markedly increases intra-articular pressure. This increased intra-articular pressure may then cause a small out pouching of posterior components of the knee joint thus producing a Baker's cyst or a popliteal cyst. If the intra-articular pressure is persistently high the cyst may then rupture or dissect into the calf or into the posterior thigh. An unruptured popliteal cyst can compress superficial

venous flow from the lower leg and produce dilation of superficial veins along with edema.[42] Rupture of the joint along with extravasation of the fluid into the calf can present with swelling and tenderness along with systemic signs of fever with leukocytosis. This can be differentiated from its differential diagnosis of acute thrombophlebitis by the appearance of a crescentric hematoma which occurs beneath one of the malleoli of the ankle.[43]

Ankles and Feet:

Ankle involvement is generally mild in patients with RA but damage occurs in severe progressive forms of the disease. Clinical presentations include cystic swellings anterior and posterior to the malleoli. In rheumatoid arthritis the inflammation and proliferation which occurs in the disease affects the joints by stretching and eroding the ligaments in the ankle thus affecting the stability of the joint. This can result in incongruity which can progress to pronation deformities along with eversion of the foot. The Achilles tendon can be involved by the formation of rheumatoid nodules on it or if diffuse granulomatous in the tendon causes spontaneous rupture.[44] Patients with RA tend to have more pain when walking on an uneven ground due to subtalar joint involvement which is commonly involved. As the eversion progresses in the subtalar joint it can lead to subluxation and lead to rocker bottom foot deformity. Disease of the mid foot can lead to collapse of the arch causing difficulty in walking. Metatarsophalangeal joints are frequently involved in RA and are the initial sites of erosions in many patients. Downward subluxation of the metatarsal heads can occur after the MTP joints become involved which produce “cock-up” toe deformities of the proximal interphalangeal joints. If the disease continues untreated it can lead to hallux valgus and bunion formation. Sometimes cystic collections develop under the MTP joints.[45]Patients who have for a chronic period of time subluxation of metatarsal heads can develop pressure necrosis on the plantar surfaces of the feet. Also those who present

with subluxation of MTP joints develop ulceration which occur over the PIP joints that protrude dorsally (hammer toes). The net result of this is increased pressure on the MTP joints which causes a sensation described as "walking on marbles" by the patients. Changes caused by the disease include stretching of the intermetatarsal joint ligament in response to inflammation, anterior migration of the plantar fat pad, spreading of the forefoot and dorsal subluxation of toes which is followed by plantar subluxation of the metatarsal heads.[46] DIP joints of the foot are not usually affected in RA. Tarsal tunnel syndrome occurs in RA patients and cause foot pain.

3.6.2 EXTRA ARTICULAR MANIFESTATIONS

Around 40% of patients with rheumatoid arthritis tend to develop extra-articular manifestations.[47]The risk ratio of mortality which is seen in RA patients who also have extra-articular manifestations is five times more than the patients who do not have the same. Patients with RA particularly tend to have increased risk of premature death due to cardiovascular disease.[48] Other factors which have been found to be associated with extra articular manifestations are smoking[49] and HLA DRB1.[50] Rheumatoid nodules also tend to have associations with severe extra-articular disease.

1. Constitutional features:

Fatigability and weight loss are frequently present in the early stages of the disease.

2. Rheumatoid nodules:

Rheumatoid nodules are predominantly present in sero-positive patients rather than sero-negative patients. The most common sites are elbows, finger joints, ischial and sacral prominence, occipital scalp and Achilles tendon.

3. Haematological manifestations:

Anaemia in RA is caused by a number of factors like abnormal iron metabolism, chronic inflammation and increased phagocytosis of RBC in spleen and synovium. Though the actual cause is not known, thrombocytosis is frequently seen in RA. Sometimes thrombocytopenia is seen due to either drug therapy or as a part of Felty's syndrome. Eosinophilia has been found to be associated with extra-articular manifestations including pulmonary complications.[51]

4. Felty's syndrome:

Felty's syndrome is defined as RA in combination with splenomegaly and leucopenia. It is often present long standing RA. It is more commonly seen in seropositive RA and is associated with nodular deforming RA. As a result of leucopenia, bacterial infections are common and they increase the mortality rates.

5. Hepatic abnormalities:

Increased liver function abnormalities are also found commonly in RA and they parallel the haematological changes in active RA such as anaemia, thrombocytopenia and a raised ESR. The difficulty arises in distinguishing

raised LFT due to drugs like methotrexate and NSAIDS to LFT raise due to the disease per se. Around 65% of the patients with Felty's syndrome present with hepatomegaly.[52]

6. Pulmonary involvement:

Pulmonary involvement is more commonly seen in males than in females with RA. Pleural involvement by the way of pleuritis is frequently seen though sometimes pleural effusions are also seen. Parenchymal pulmonary nodules are frequently seen in seropositive RA and are generally asymptomatic. In RA patients exposed to silica and coal dust, Caplan syndrome, which is pulmonary nodulosis and pneumoconiosis, is seen. Rheumatoid interstitial pulmonary fibrosis is found frequently found more in men with long standing, nodular, seropositive RA and in smokers.[53]Few cases of Bronchiolitis oblierans organising pneumonia has been documented in patients with RA and they generally tend to have a good prognosis. However obliterative constrictive bronchiolitis generally tends to have a poor prognosis.[53]Patient could have large airway obstructive disease which can be due to the primary disease or due to other risk factors.

7. Cardiac involvement:

There are a number of cardiac presentations in RA and it is possibly due to various mechanisms like vasculitis, serositis, nodule formation, amyloidosis, valvulitis and fibrosis. The most common finding seen in cardiac patients with seropositive RA with nodules is pericarditis. Myocardial disease due to nodular

granulomatous disease is also seen in RA. There is also increased risk of ischemic heart disease and congestive heart failure.[54]

8. Neurological involvement:

Patients with RA can present with mononeuritis multiplex or diffuse sensori-motor neuropathy caused by vessels neuropathy. Nerve compression due to peripheral entrapment neuropathy occurs and they correlate with the severity of local synovitis. The frequently involved nerves include are median, posterior tibial, ulnar and posterior interosseous branch of the radial nerve. Sometimes cervical neuropathy occur secondary to atlanto axial subluxation.

9. Muscular involvement:

There can be muscular atrophy which occurs secondary to joint inflammation, medications, nutrition problems or neurological dysfunction.

10. Renal involvement:

Rarely patients with RA have renal involvement in various forms like vasculitis, glomerulitis, membranous nephropathy or secondary reactive amyloidosis. Mesangio proliferative glomerulonephritis is considered as part of systemic organ involvement in RA.

11. Amyloidosis:

Rarely long standing RA can be complicated by secondary amyloidosis. Few studies state that 0.7% patients of rheumatoid arthritis have clinical visceral amyloidosis.[47]The commonly involved organs in vasculitis include heart, liver,

kidney, spleen, skin and intestines. The most significant of these reactive organ manifestations is renal disease.

12. Rheumatoid vasculitis:

RA is closely associated with small vessel vasculitis. Studies have demonstrated subclinical vasculitis in seropositive patients and immune deposits in affected skin and labial salivary glands.[55] HLA DRB1 alleles, mainly the B1 0401 homozygotes have been seen to be associated frequently with vasculitis. Though it is a rare feature in RA, systemic vasculitis tend to indicate a poor prognosis.[47] Vasculitis generally involves the skin causing nail fold infarcts, gangrene of the digits and ulcers in the leg.

13. Ocular manifestations:

Ocular manifestations are one of the most common extra articular manifestations seen in patients with RA and it occurs in about 25% of the patients.[56]These include dry eye (sicca), keratitis, keratolysis, episcleritis, scleritis among others.

Variants of the disease:

PALINDROMIC PATTERN:

Here the disease usually begins with pain in a single joint or periarticular tissue. Symptoms then worsen over a period of hours to few days and are associated with erythema and swelling. Symptoms then resolve in a reverse sequence leaving no residual deformities. Though they are not typically RA,

studies show that 85% of these patients progressed over a period of time to seropositive RA involving multiple joints.[57]It has now been found that use of antimalarials for this disease reduces the chances of progression to RA.[58]

INSIDIOUS ONSET IN OLD INDIVIDUALS:

People who develop RA after 65 years of age frequently have stiffness, limb girdle pain along with diffuse swelling in the hands, wrists and forearms. Onset that mimics either polymyalgia rheumatica or remitting seronegative synovitis with pitting edema (RS3PE) can also be the presentation. Patients are less likely to have subcutaneous nodules or RF positivity at the onset of disease. This is despite the fact that RF is highly prevalent in the general population in this specific age group. Generally, these patients tend to have a more benign course when compared to younger people with RA. Though the onset is slow, stiffness is often incapacitating. As they tend to have associated osteoarthritis there is significantly greater scores for joint space narrowing and osteophytes at baseline when compared to younger RA patients.[59]

Arthritis Robustus:

Arthritis robustus is more of an unusual reaction in patients with RA than an unusual reaction of the disease.[60] Usually patients are men whose have proliferative synovitis frequently with deformity, which causes little pain and disability. Patients are generally athletic and generally keep working. Periarticular osteopenia is rare, but new bone proliferation occurring at joint

margins near erosions of bones and cartilages are common. Bulky subcutaneous nodules and subchondral cysts can develop.

3.7 ASSESSMENT OF SEVERITY OF THE DISEASE:

In trying to sort out the relative roles of various disease manifestations, compared with various non-disease factors, to generate disability in RA, hypothetical models were proposed to predict disability in RA using socio-cultural, demographic and clinical features of a cohort of RA patients.[61] Though their methods was not useful to explain the dynamics of disability in RA in 41% of cases, 33% was explained by disease related factors and 26% was explained by non-disease factors such as depression and psychological status. Various studies have discussed the following disease factors, which tend to correlate with a poor prognosis in patients with RA and a greater likelihood of severe joint involvement.

1. Positive ACPA in serum
2. Positive RF in serum[62]
3. Elevated Health Assessment Questionnaire level of disability.[63]
4. Rheumatoid nodules.[64]
5. Depression.[65]
6. Persistent ESR elevation (surrogate for disease control).
7. Presence of a shared epitope (QKRAA) in the class II major histocompatibility genes.

HEALTH ASSESSMENT QUESTIONNAIRE

A. How often is it PAINFUL for you to:

	Never	Sometimes	Most of the Time	Always
Dress yourself?				
Get into and out of bed?				
Lift a cup or glass to your lips?				
Walk outdoors on flat ground?				
Wash and dry your entire body?				
Bend down to pick up clothing from the floor?				
Turn faucets on or off?				
Get into and out of a car?				

B. How much pain have you had in the PAST WEEK? *(mark the scale)*

No pain

Pain as bad as it could be

0 100

ASSESSMENT OF DISEASE SEVERITY IN INDIVIDUAL PATIENTS

Assessment of disease activity and its progression in a patient is very different from prognosis. Prognosis extrapolates and predicts an outcome from a known set of indices and the degree of measured activity of the disease. Assessment however, is the accurate evaluation of the disease at present in a patient or of the disease progression over a period of time. It was found that use of three or more assessment measures together provides us with a graph of progression of the disease in an individual that can be remedied by therapy.[66] For most patients with RA, a self-report questionnaire based on degrees of difficulty in performing activities of daily living correlates well with other widely accepted severity indices. The limitation of this form is however there is a failure to detect clinical improvement in those patients with very small impairment in activities of daily living. However these are still used now as they are very convenient. In some patients, more comprehensive joint counts are needed especially when biologics, DMARDS or surgery is planned. The

Thompson index used a few joints and weights from each of these joints to reflect the joint surface area, giving us a measure of the "burden of synovitis."[67]Radiological investigations are used to detect the severity and the problems of long standing RA. Various indices like erosions, joint swelling and fractures are used. The correct choice of imaging is important in assessment of the destructive lesions of RA. Though USG and MRI are used to detect early changes X Rays continue to the cost effective first line investigations and various severity scales use X Rays.

CLINICAL SEVERITY SCALES:

A major problem in RA is having valid reproducible measures of disease activity measurement for initial evaluation as well as for determining prognosis and remission and then routinely measuring and following those in a clinic. Unfortunately, there is no single specific examination finding or laboratory investigation that satisfactorily measures disease severity and activity.
Many measures and various scales have been proposed over a period of time and all of these are composite measures that include information derived various features like some predetermined combination of joint examinations, physician and patient assessment of disease activity, patient function and morbidity and laboratory measures of inflammation like erythrocyte sedimentation rate or C-reactive protein . The American College of Rheumatology (ACR) has recently endorsed a fixed list of disease activity scales and measures that have been found to correlate with outcomes. The table

below gives a partial list of some of the better known of these measures. There is weakness and strengths in each of these scales.[68] Few of these tests rely only on data from the patients, while some have joint counts by the doctors while others require laboratory investigations. As time for examination is less with many patients scales with lesser number of joints (DAS28), based fully on patient data(RAPID) or those which do not require investigations (Clinical Disease Activity Index) are more in vogue. There is a very high correlation among these measures, so currently it is more important that disease activity is measured and less important which of these measures are used.

		Thresholds of Disease Activity			
Instrument	Score Range	Remission	Low	Moderate	High
Disease Activity Score in 28 joints (DAS28)	0-9.4	≤2.6	≤3.2	>3.2 and ≤5.1	>5.1
Simplified Disease Activity Index (SDAI)	0.1-86.0	≤3.3	≤11	>11 and ≤26	>26
Clinical Disease Activity Index (CDAI)	0-76.0	≤2.8	≤10	>10 and ≤22	>22
Rheumatoid Arthritis Disease Activity Index (RADAI)	0-10	≤1.4	<2.2	2.2 and ≤4.9	>4.9
Patient Activity Scale (PAS or PASII)	0-10	≤1.25	<1.9	≥1.9 and ≤5.3	>5.3
Routine Assessment Patient Index Data (RAPID)	0-30	≤1	<6	≥6 and ≤12	>12

DAS28 SEVERITY SCALE

The initial design of the DAS goes back to 1983. Initially at that time a modification of an existing disease activity index was used in small clinical trials.[69] DAS was first introduced by the Department of Rheumatology, University of Nijmegen In 1983 after assessing various data from their patients and determining the prognostic indicators among them. As a golden standard for disease activity was lacking at that time, patients were divided as having high or

low disease activity depending on the joint decision of the clinician and the patient. After that it was investigated which variables among the many, and in particular which combination of variables discriminated best between these two different disease states. This resulted in the Disease Activity Score (DAS) which was released in 1983.[70,71]The initial DAS included 44 swollen joints count, the Ritchie articular index, the Erythrocyte Sedimentation Rate and a general health assessment based on a Visual Analog Scale. After further validation of the new 28 non-graded joint count for both tenderness and swelling, DAS28 was formed.[72]The results of both the DAS and the DAS28 have been found to not be directly interchangeable as in the DAS there is a range which varies from 1 to 9 and in the DAS28 the range is from 2 to 10. So a transformation formula has been given by which we can calculate the DAS28 from the DAS value: DAS28= (1.072 x DAS) + 0.938.[73]Most studies show that serial measurements of the DAS28 is a strong predictors of physical disability and morbidity.[74] However differences do exist about whether they are predictors for radiological progression with some studies showing a positive correlation and some showing negative correlation.[75,76] However the present thought is that clinical severity scales shows the active inflammation and morbidity and does not correspond well with the chronic erosive process.[8] Based on the DAS scales, response criteria have been developed to determine if patient is responding to treatment: the EULAR response criteria. The EULAR response criteria include both changes in disease activity and current disease

activity.[77,78]To be designated as responders, patients should have a significant change in DAS scores and also low current disease activity. Three categories are defined: good, moderate, and non-responders. A cut-off level of the DAS of 1.6 or a DAS28 of 2.6 corresponded with the patient being in remission after treatment.[79]

COMPONENTS OF DAS28[80]

1. The number of tender joints of the 28 joints that are measured (tender28)
2. The number of swollen joints of the 28 joints that are measured (swollen28)
3. The Erythrocyte Sedimentation Rate (ESR) given in mm/hour
4. The patients' general health (GH) score or global disease activity value measured on a Visual Analogue Scale (VAS) of 0 to 100 mm.

Swelling of joints (SJC):

Soft tissue swelling, detectable along the joint margin is considered. Synovial effusion generally means the joint is swollen. Bony swelling , deformities and oedema surrounding the joints do not constitute joint swelling.Fluctuation is generally a characteristic feature of swollen joints. Joint swelling can influence the range of joint movement (for eg: decreased dorsiflexion of the wrist, or decreased elbow extension). This can be used in determining the presence of swelling. [81]

Tenderness (TJC) of joints:

Pain in a joint under defined circumstances which are

1. Pain at rest with pressure (seen in MCP and wrist joints)
2. Pain on movement (shoulders)
3. From questioning about joint pain

The DAS28 can be calculated using the following formula [82]:

DAS28=0.56*√(tender joints) + 0.28*√(swollen joints) +0.70*Ln(ESR/CRP) + 0.014*VAS

This calculation might not be easy, but there are various calculators which provide the value immediately. Based on these values patients can be classified into 3.

1. **DAS28 SCORE <3.2 – LOW DISEASE ACTIVITY**
2. **DAS28 SCORE 3.2-5.1 – MODERATE DISEASE ACTIVITY**
3. **DAS28 SCORE >5.1 – SEVERE DISEASE ACTIVITY**

The EULAR Response criterion is shown below.

A decrease in DAS28 score of 0.6 or less is generally considered to show a poor response, while decreases that are greater than 1.2 points indicate a

moderate or good response, but it is dependent on whether an individual's DAS28 score at the end point is above or below 3.2 respectively.[83,84]

DAS28 improvement → / Present DAS28↓	> 1.2	> 0.6 and ≤ 1.2	≤ 0.6
≤ 3.2	good response	moderate response	no response
> 3.2 and ≤ 5.1	moderate response	moderate response	no response
> 5.1	moderate response	no response	no response

RADIOLOGICAL SCALES

Evaluation and interpretation of structural joint damage on repeated radiography is one of the central outcome measures in patients with rheumatoid arthritis, both in clinical trials and routine clinical management.[85,86] Generally radiological investigations give a permanent as well as comparative measure of damage in rheumatoid arthritis. X Rays of hands and feet have always been an important and fundamental part in the evaluation of RA course and its response to medication over the last sixty years.[87] The long-term severity and problems of RA was seen in longitudinal studies of various clinical cohorts that showed that the disease has continuous radiographic progression when seen in follow-ups over 20 years and more.[88,89] The efficacy of various DMARDs has been traditionally viewed by their effect in slowing down or reversing radiological

damages.[90] Also milder radiographic progression of RA present, compared to previous times shows the improved outcomes of RA due to newer modes of treatment.[91,92]Recent advances in the field of radiology has resulted in newer methods of investigations like USG and MRI. These investigations are definitely valuable and have been found to be more sensitive than radiographs in finding early structural changes in joints and other structures. However, the availability of these, especially in the developed countries along with the high costs limits the use of these investigations in daily clinical practice. Therefore clinical trials tend to mainly rely on radiographs rather than other imaging technology.[93] Earlier radiographs were scored by the Steinbrocker scoring system9 which has a global damage score to both hands and wrists on a four-point scale starting from I (minimal damage) to IV (severe damage).[94]The grade was measured by the worst change in any joint and so the score was biased toward the most affected joint. The Kellgren method, which was similar to the previously mentioned Steinbrocker method: a global grade was there as the addition of abnormalities of all the joints in both the hands and wrists.[95] The two most commonly used measures of radiographs now are that of Sharp[96] and Larsen.[97,98] These scales provide a continuous quantitative scale that extends for more than 100 units unlike other scales that give just qualitative assessment of the changes. The Sharp method consists of separate scores for both erosions and joint space narrowing and the Larsen method gives a global

score for each involved joint. Among all these scales because of the better ability of the Van der Heijde modification of the Sharp method [99] in detecting changes that occur over time in RA, at present this is most often used in clinical trials.[100]

The Sharp Method and Van der Heijde modification of Sharp method

The Sharp method initially consisted of radiographs of both hands and wrists and took into account several features like periosteal reaction, osteoporosis, cortical thinning, osteophytes formation, sclerosis, cystic changes, ankylosis, surface erosions and joint space narrowing.[96] Later due to various reasons, five of these were omitted from the final score.

- Periosteal reaction was considered too unusual.
- The quality of radiographs obtained was generally too poor to find cortical thinning.
- Osteoporosis, osteophyte forrmation and sclerosis are now considered to be secondary changes.

The final Sharp method of scoring, thus includes just two scores, one for erosions and one for joint space narrowing.[101]In the original Sharp method, erosion scores were between 0 to 5 and a number between these was given to each joint that was taken based on the number of erosions. “5” denoted total joint destruction.

Joint space narrowing is scored from 0 to 4 as follows [102]:

0 - Normal

1 - Focal narrowing

2 - Reduction of less than 50% of total joint space

3 - Reduction of greater than 50% of total joint space

4 - Ankylosis

The total number and selection of the joints in the Sharp score changed from including hands and wrists to hands (including wrists) and feet. In the Van der Heijde modification of the Sharp score, 16 joints from each hand and wrist was included in the erosion score. For the feet, each side of the 10 MTP joints and the 2 interphalangeal joints of the big joints alone are evaluated.[103]

The Van der Heijde modification of Sharp defines erosions as[104]:

- 0 – Normal (no features)
- 1 - Discrete erosions seen
- 2 to 3 - Larger erosions present. It is further graded as 2 or 3 depending on the surface area involved.
- 4 - Erosions extend over the middle of the bone.
- 5 - Complete collapse of the involved joint.

Van der Heijde score for joint space narrowing includes 15 places from the hands with wrists and six areas from both the feet. Joint space narrowing is generally scored similar to the original definition given by Sharp, as shown above. The maximum erosion score obtainable is 160 for hands with wrists and 120 for feet. Similarly the maximum joint space narrowing score for the hands

is 120 and 48 for feet. So the total van der Heijde radiographic score is from 0 to 448.[103]

3.8 ANTIBODIES IN RA

Autoantibodies are proven to be very useful tools in the diagnosis and prediction of the various autoimmune rheumatic diseases. Emerging recent data about various autoimmune connective tissue disorders have shown that clinical evolution of the disease from a preclinical phase to a clinical disease is generally marked by changes in the immune response, with autoantibodies formed which are directed against different antigenic targets at various disease phases.[105] Although many of these diseases have traditionally been characterised by highly phenotype-specific autoantibodies like anti dsDNA in systemic lupus erythematosus and anti-topoisomerase-1 antibodies in diffuse scleroderma, the discovery of specific autoantibody for RA lagged behind. However there has been rapid progress recently after citrullinated proteins were found to be specific targets for autoantibodies in RA. The two main set of antibodies at present are rheumatoid factors (RFs) and anticitrullinated protein autoantibodies (ACPAs). Out of these the more commonly available and used is the Rheumatoid Factor, which is also used in this study.

RHEUMATOID FACTOR

Initially the Rose-Waaler agglutination test was introduced which first suggested the presence of autoantibodies in rheumatoid arthritis in the early

1940s.[106] At that time serum was taken from patients with RA it was found to cause agglutination of blood cells of sheep, which previously had been sensitized by subagglutinating doses of rabbit's anti-sheep erythrocyte antibodies.[107] Later it was shown that the assays were actually detecting immunoglobulin M (IgM) antibodies in patients with RA against the Fc portion in IgG.[108] Further improvements resulted in RF assays in various methods which were more convenient but had the equivalent sensitivity and specificity like radioimmunoassay, ELISA and nephelometry methods. RF positivity is also seen in 1% in younger individuals moving up to 5% in individuals who are older than 70 years and also in patients with diseases other than RA, like Sjögren's syndrome, cryoglobulinemia and chronic infections.[109,110] Detection of IgA and IgG RFs along with evidence of somatic hypermutation have provided the thought that some RFs in rheumatoid arthritis are T cell dependent.[111,112] There are differences over the uses of measuring all three RFs compared to one. There are some studies which suggest that measuring all 3 RFs increase the specificity.[113] However a recent study has showed that measuring of all 3 assays do not improve the sensitivity and specificity when compared to single assays.[114] There are a few studies which determine differences between the various types of RF. Some state that IgM RF helps in predicting development of RA while some studies states that IgG RF correlates with radiological progression though other studies seem to differ.[115] IgM RF remains the most sensitive antibody. Also early onset of RF positivity in

patients with rheumatoid arthritis is found to be correlating with increased severity of the disease probably due to the role of the antibodies in amplification.[116]

3.9 DIAGNOSIS

There is no single test to confirm the presence of RA. A patient is diagnosed as having RA based on a multitude of factors like relevant history, supportive clinical features and supporting immunological investigations along with exclusion of other similar diseases. For the sake of uniformity all over the world and for the sake of clinical studies American College of Rheumatology criteria for RA was published in 1987. Though it was not used for individual cases for treatment, the requirement of synovitis needing to be greater than 6 weeks helped in eliminating a number of patients who had transient synovitis. This ACR classification was again revised in 2010 by the EULAR (European League Against Rheumatism) and ACR.[117] The major differences were that the newer classification stressed on earlier diagnosis and hence more importance was given to serology and less to the type of clinical presentation. It also considered the newer modes of radiological investigations like USG and MRI which was not considered in the previous criterion. As it a new criterion, the long term efficacy of this criterion is not yet known and is the topic of various studies all over the world.

1987 Revised American Rheumatism Association Criteria for Classification of Rheumatoid Arthritis

Criterion	Definition
Morning stiffness	Morning stiffness in and around the joints lasting at least 1 hour before maximal improvement
Arthritis of ≥3 joint areas	At least 3 joint areas simultaneously having soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician (the 14 possible joint areas are [right or left] PIP, MCP, wrist, elbow, knee, ankle, and MTP joints)
Arthritis of hand joints	At least 1 joint area swollen as above in wrist, MCP, or PIP joint
Symmetric arthritis	Simultaneous involvement of the same joint areas (as in criterion 2) on both sides of the body (bilateral involvement of PIP, MCP, or MTP joints is acceptable without absolute symmetry)
Rheumatoid nodules	Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions, as observed by a physician
Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method that has been positive
Radiographic changes	Changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to involved joints (osteoarthritis changes alone do not qualify)

American College of Rheumatology Criteria	Sensitivity (%)	Specificity (%)
Morning stiffness	68	65
Arthritis in >3 areas	80	43
Arthritis of the hand joints	81	46
Symmetric arthritis	77	37
Rheumatoid nodules	3	100
Rheumatoid factor	59	93
Radiographic change	22	98

	Persistent Nonerosive Versus Self-Limiting		*Persistent Erosive Versus Persistent Nonerosive*	
Clinical or Laboratory Variable	**Odds Ratio**	**Score**	**Odds Ratio**	**Score**
Symptom duration at first visit				
>6 weeks, <6 months	2.49	2	0.96	0
>6 months	5.49	3	1.44	0
Morning stiffness >1 hour	1.96	1	1.96	1
Arthritis in ≥3 joints	1.73	1	1.73	1
Bilateral MTP compression pain	1.65	1	3.78	2
Rheumatoid factor positivity	2.99	2	2.99	2
Anticitrullinated protein antibody positivity	4.58	3	4.58	3
Radiographic erosions (hands or feet)	2.75	2	Infinite	Infinite

*For classification purposes, a patient is said to have RA if he or she has satisfied at least four of the seven criteria. Criteria 1 through 4 must be present for at least 6 weeks. Patients with two clinical diagnoses are not excluded. Designation as classic, definite, or probable RA is not to be made.

MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal; RA, rheumatoid arthritis.

ACR/EULAR CRITERIA FOR RA (POSITIVE- 6 OR MORE)

Joint Involvement*	**(0-5)**
1 medium to large† joint	0
2-10 medium to large joints	1
1-3 small‡ joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints§ (at least one small joint)	5
Serology‖¶	**(0-3)**
Negative RF **AND** negative ACPA	0
Low-positive RF **OR** low-positive ACPA	2
High-positive RF **OR** high-positive ACPA	3
Acute Phase Reactants‖#	**1**
Normal CRP **AND** normal ESR	0
Abnormal CRP **OR** abnormal ESR	1
Duration of Symptoms**	**(0-1)**
<6 weeks	0
≥6 weeks	1

4. MATERIALS AND METHODS:

4.1 INCLUSION CRITERIA:

A total of 100 patients who attended the outpatient clinic of the Department of Rheumatology in Government Kilpauk Medical College and Hospital were consecutively selected for the present study during the period of December 2011 – June 2013. The patients who were selected for the study was diagnosed to have rheumatoid arthritis based on the 2010 ACR/EULAR Criteria for diagnosing RA. These patients had 6 or more points in the criteria.

4.2 EXCLUSION CRITERIA:

1. Collecting a proper history has been the most important part of the study. As presence of the disease in the patient as well as treatment taken during the period tends to affect both the clinical severity scales as well as the progression of radiological persons, patients with previously diagnosed RA, whether on proper follow up or not, were omitted from the study.

2. Patients with history as well as clinical features of other diseases which affected the joints were also excluded from the study as it would be difficult to differentiate if the signs were due to RA or any other concomitant disease. This included diseases like osteoarthritis, post viral arthlagia, gout and hypothyroidism.

3. Patients with presence of features or antibodies suggestive of autoimmune connective tissue disorders other than rheumatoid arthritis were also excluded from the study as the cross positivity of various antigens need to be taken into account.

With the above given inclusion and exclusion criteria, patients suffering exclusively from rheumatoid arthritis were included in the study.

4.3 DATA COLLECTION

First the entire details of the study were described to each individual patient. Their role in the study was fully explained and their willingness to participate in the study obtained along with a written consent.

4.3.1 History: An exhaustive and detailed history was obtained from the patient. This included history of their various symptoms pertaining to RA and also other unrelated symptoms. All significant past histories and treatment histories were also noted.

4.3.2 Clinical examination: In a well lit room patient was examined in full detail. All relevant clinical finding were noted. The individual joints were examined and patients were also examined for extra-articular manifestations. The joint count for swelling and tenderness of joints were done to calculate the DAS28 score. Each patient's counts were entered into a proforma and the individual scores calculated.

DAS28 form

Patient name …… Date of Birth ____-____-_____

Observer name …… Date ____-____-_____

		Left		**Right**	
		Swollen	Tender	Swollen	Tender
Shoulder					
Elbow					
Wrist					
MCP	1				
	2				
	3				
	4				
	5				
PIP	1				
	2				
	3				
	4				
	5				
Knee					
Subtotal					
Total		Swollen		Tender	

How active was your arthritis during the past week?

(Please mark the degree of activity on the scale below by placing a vertical line |)

Not active at all _____ **Extremely active**

Swollen Joint Count (0-28)	
Tender Joint Count (0-28)	
ESR	
VAS disease activity (0-100mm)	

DAS28 = 0.56*√(t28) + 0.28*√(sw28) + 0.70*Ln(ESR) + 0.014*VAS

The above mentioned form was obtained from www.das28.nl, which is the official website for DAS28 and the same is used in many clinical trials. Using the calculator given in the same aforementioned website, the individual scores were calculated for each patient and they were divided into 3 categories based on the scores

Score < 3.2 Low disease activity

Score 3.2 -5.2 Medium disease activity

Score > 5.2 High disease activity

4.3.3 RADIOLOGICAL EXAMINATION: The patients were then taken to the Department of Radiology for radiographs of their hands and feet. Positioning of the hands and feet were well standardised with the same technician being used for all the patients. The x-ray tube was positioned 100 cms from the cassette and the beam was centered on the 3rd metacarpal for the hands and the 3rd MTP joint for the feet.

For the hands, the elbows were in the same plane as the hands and the 3rd metacarpal was in line with the forearm and the fingers were placed flat on the table.

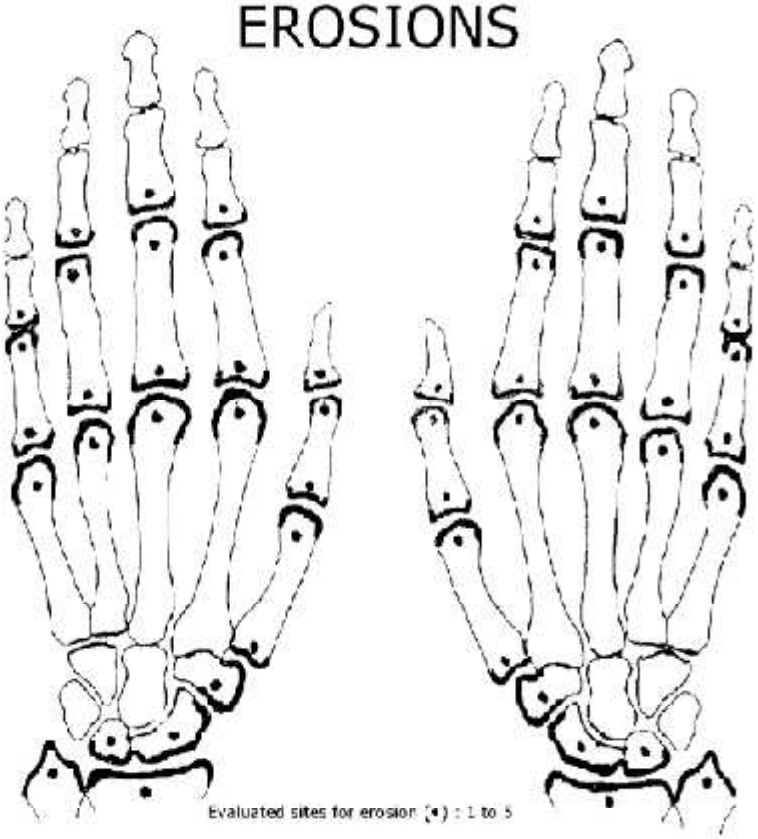
For the foot, patient was told to apply pressure of the entire foot on the table so that the foot is completely flat. The emphasis was laid more on the toes, particularly the MTP joints as the score involves these joints.

The various radiographs were studied by the Professor and HOD, Department of Radiology, Government Kilpauk Medical College and Hospital along with the primary observer and the individual scores for each patient was obtained based on the Van der Heijde modification of Sharp score. This took into account the erosions and the joint narrowing in various defined joints. Each patient's finding was denoted in the following score sheet and the total score obtained by the sum of 2 scores.

Initials of the patient's name : _____ Date : _____ Visit : 1 2 3 4 5

File CHUS : _____

EROSIONS



Evaluated sites for erosion (•) : 1 to 5

Score

Hands : _____

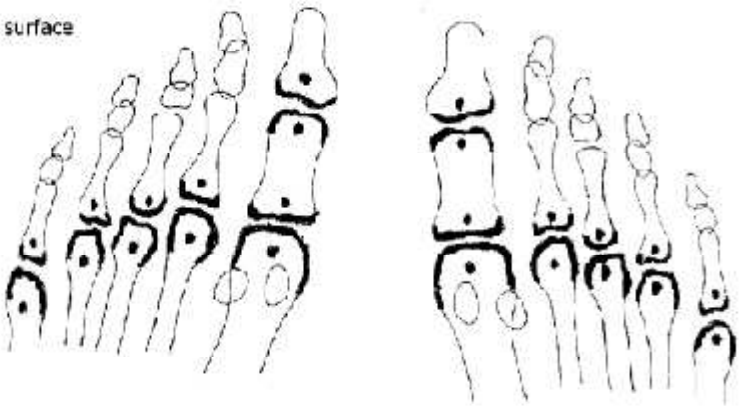
Feet : _____

Total :

SCORE

1 = Discreet lesion
2 to 4 = Surface dependant
3 = Reaches >50% of the joint surface
5 = Bone collapsus

P.S. The erosion noted can be caused by R.A. and arthrosis



Evaluated sites for erosion (•) :
1 to 10 (5 for each side of the joint)

_____ Signature of the evaluator

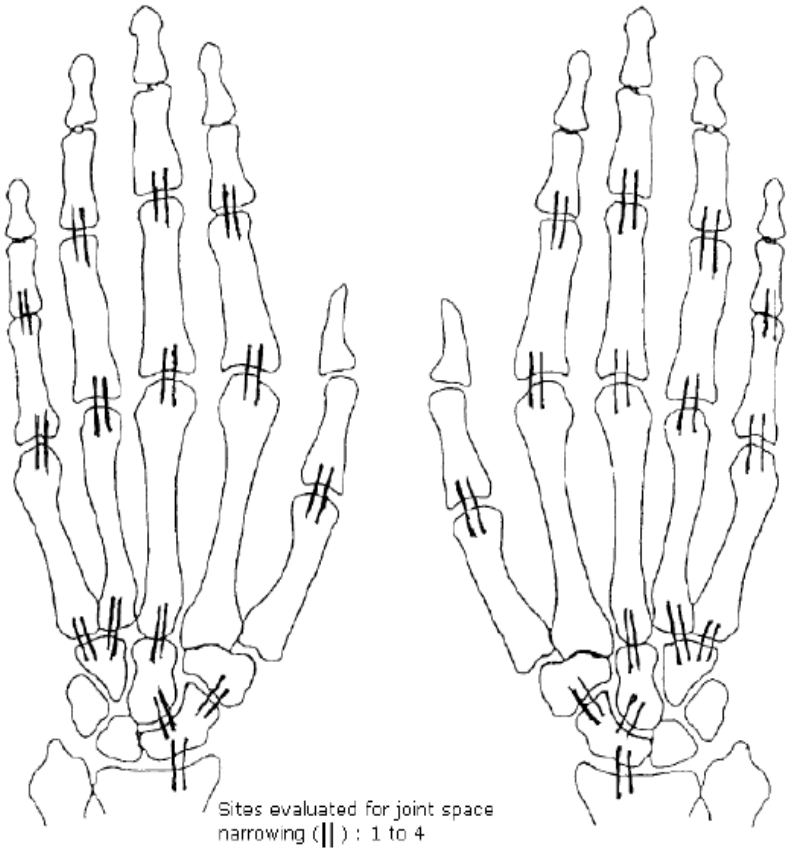
_____ Date of the evaluation

Initials of the patient's name : _____ Date : _____ Visit : 1 2 3 4 5

File CHUS : _____

JOINT SPACE NARROWING

Defined periarticular osteopenia ☐



Sites evaluated for joint space narrowing (||) : 1 to 4

Score

Hands : _____

Feet : _____

Total : _____

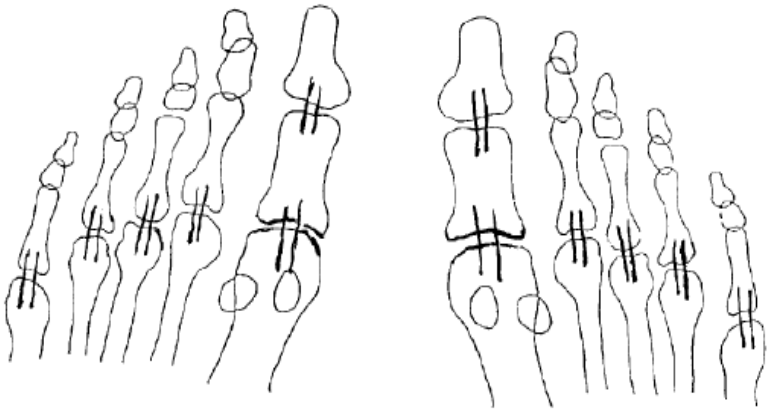
Score

1 = Focal or not important enough to quote 2

2 = >50% space left (generalized narrowing)

3 = <50% space left or subluxation

4 = Complete ankylosis or luxation

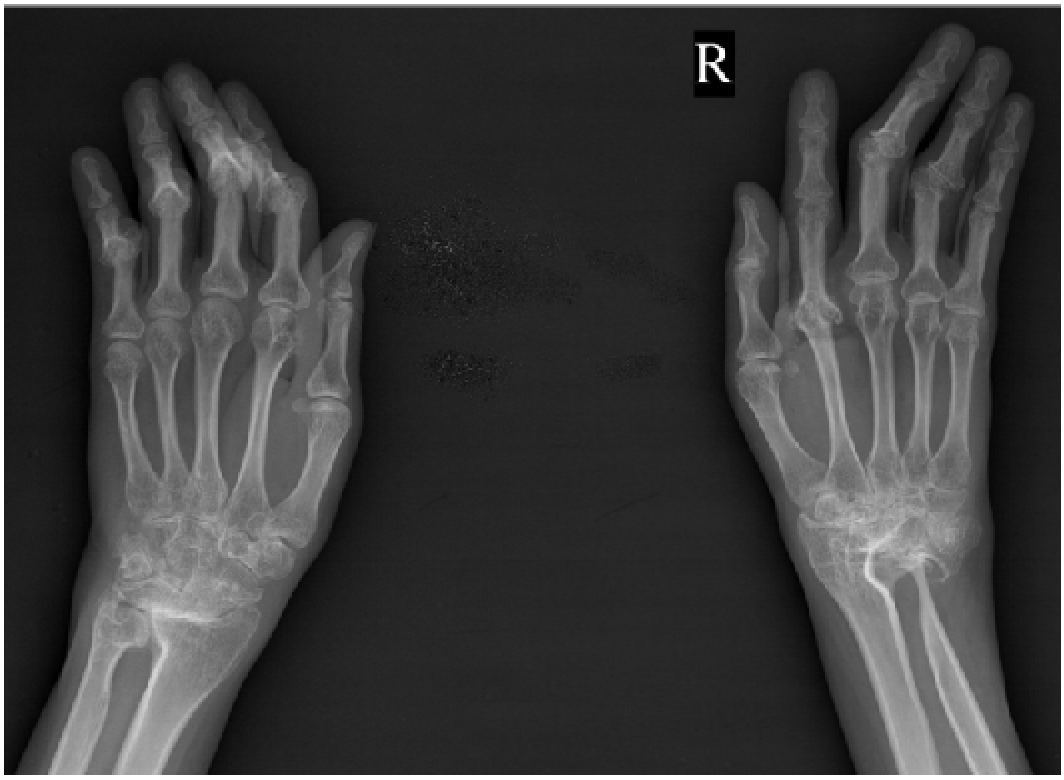


Sites evaluated for joint space narrowing (||) : 1 to 4

_____ Signature of the evaluator

_____ Date of the evaluation

Radiographs of patients involved in the study




R


R

Though there is no proper classification based on the scores, the patients were divided based on the scores into 5.

Group 1 - patients with score of O

Group 2 - patients with a score of 1 to 6

Group 3 - patients with a score of 7 to 12

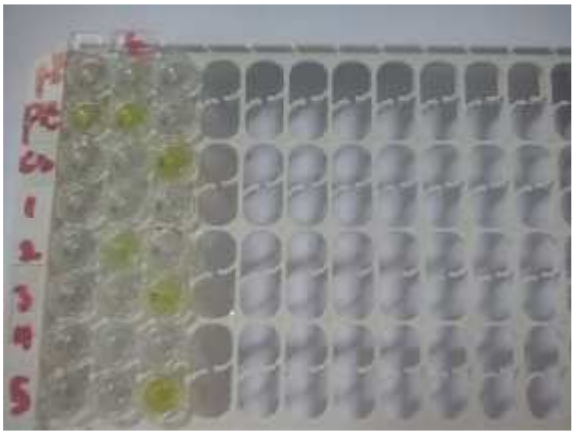
Group 4 - patients with a score of 13-20

Group 5 - patients with a score of > 20

4.3.4 BLOOD INVESTIGATIONS

All the patients underwent the regular blood investigations required for diagnosing and managing RA. This included ESR, CRP, IgM RF , anti CCP , renal function and liver function tests among others. The IgM RF positivity and negativity was checked for all the patients. Also, using aseptic precautions, 2ml of blood was withdrawn from a venupuncture site from all these patients. The blood was then centrifuged and the serum separated and stored in special containers in a freezer at -20 degrees Celsius. After all the samples were collected the serum was used to detect the IgG RF among the various patients by the ELISA reader in the Department of Rheumatology, Government Kilpauk Medical College. The patients with positive and negative IgG RF were noted.

IgG RF ELISA done is serum of patients of the study.



4.4 STATISTICAL ANALYSIS

STATISTICAL TOOLS:

The information collected regarding all the selected cases were then recorded in a Master Chart. Data analysis was done with the help of computer using **statistics software (SPSS).**

Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-squaretest was used to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A 'p' valueless than 0.05 is taken to denote significant relationship.

5. OBSERVATIONS AND ANALYSIS

A total number of 100 cases satisfying the criteria for diagnosis of RA were taken. The age and sex distribution of these patients have been illustrated in table 5.1

Table 5.1 : Age and sex distribution of RA patients in the present study.

AGE (YEARS)	No. of patients (n=100)	Sex (M: F)
0-20	2	2:0
21-30	8	3:5
31-40	24	8:16
41-50	35	7:28
51-60	21	3:18
>60	10	1:9

Out of the 100 cases taken for the study, there were 24 males and 76 females. This corresponded to a Male : Female ratio of 1:3.This correlates with various studies which shows a female preponderance of RA. This is illustrated in chart 5.1a.

The maximum cases were in the age range of 41-50 followed by the age group of 31-40 and 51-60. This correlates with various studies which show that

RA is mostly a middle age disease. The age distribution in males and females are illustrated in charts 5.1b and 5.1c.

Chart 5.1a Gender distribution of the patients.

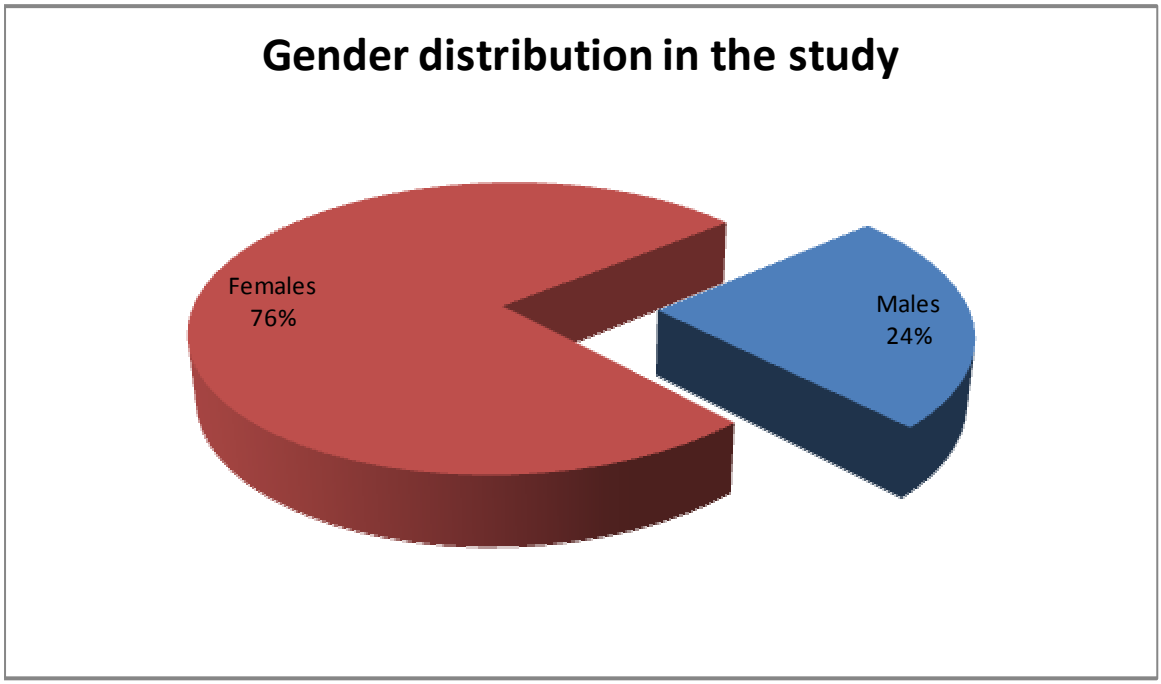
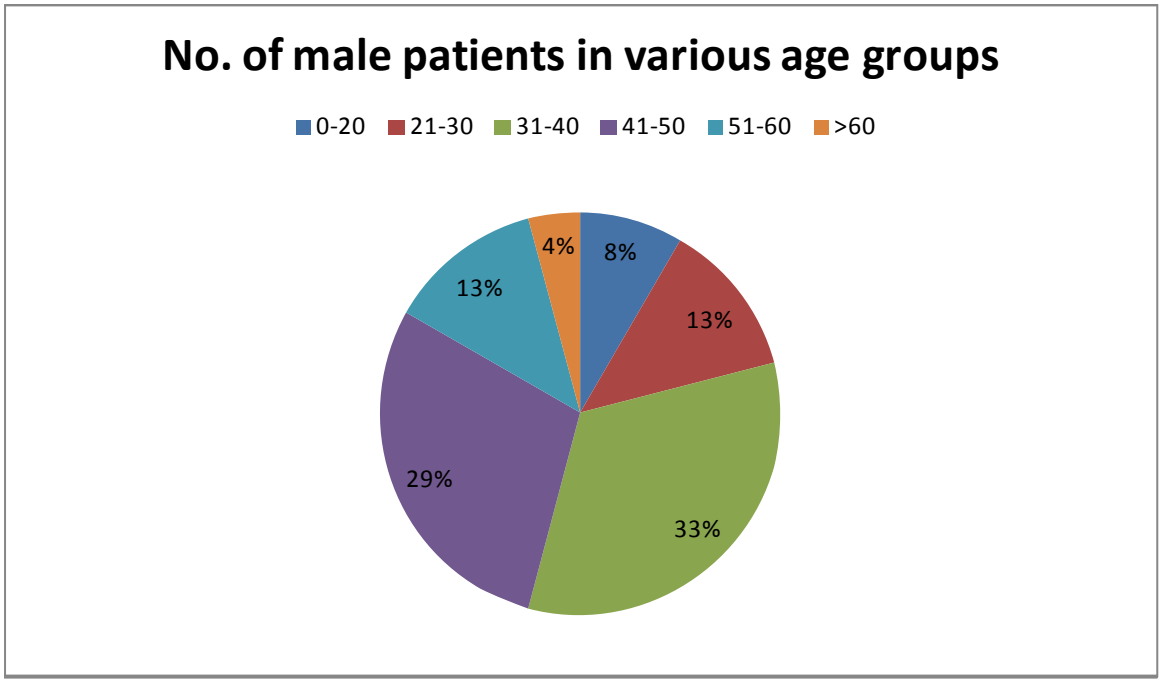
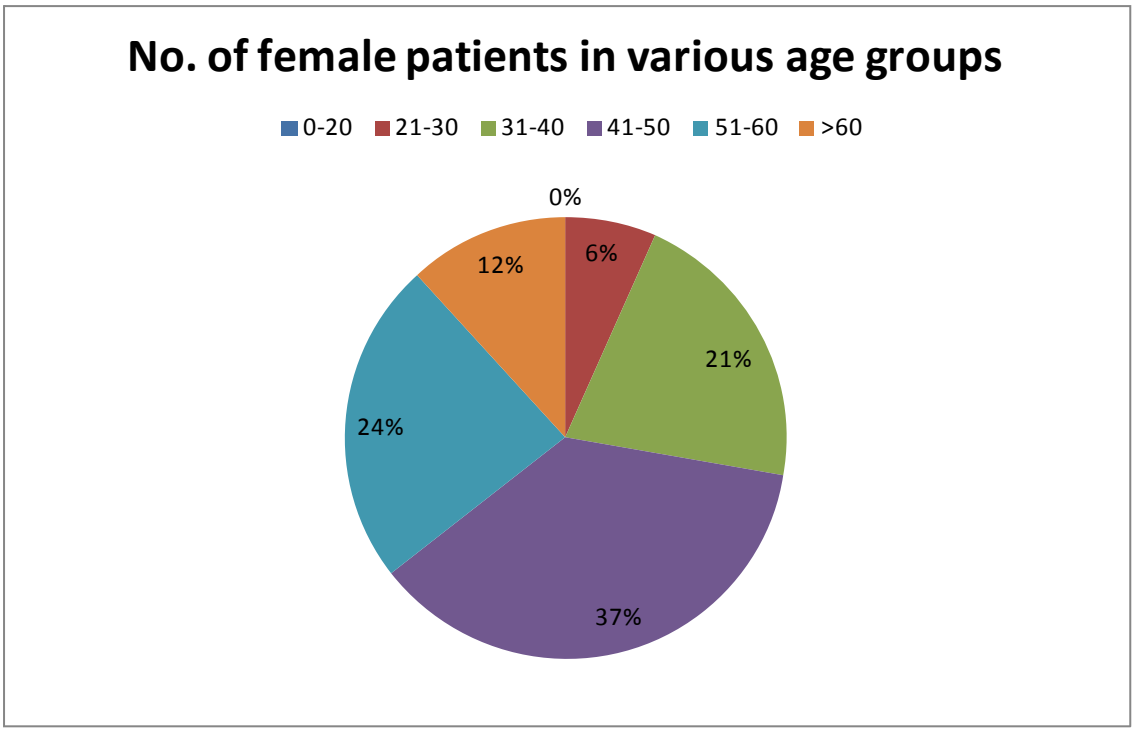


Chart 5.1b Age distribution in the Male patients.



5.1c Age distribution of female patients in the study



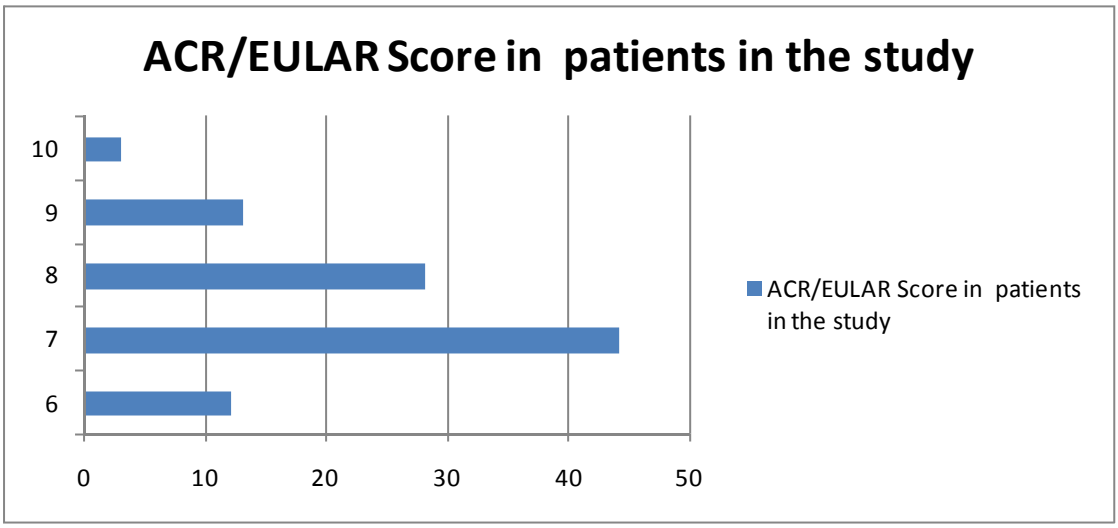
The average age of the patients in the study was seen 45.9 years and the median was 45 years. This correlates with the fact that RA is a disease of the middle age. Moreover various studies suggest that long time complications tend to increase with duration of the disease. RA tends to increase risk for other disease like atherosclerosis and this is even more significant as elderly people already have an increased risk for most of these diseases. The gender distribution again correlates with the general literature about RA. Almost all connective tissue disorders tend to occur more in females compared to males.

All the patients were taken as suffering from RA based on the ACR/EULAR score. The distribution of the score in the 100 patients was observed and the distribution is shown in table 5.2 and chart 5.2

Table 5.2: Distribution of ACR/EULAR Score in RA patients in the study.

ACR SCORE	No. of patients
6	12
7	44
8	28
9	13
10	3

Chart 5.2: Distribution of ACR/EULAR Score in RA patients in the study.

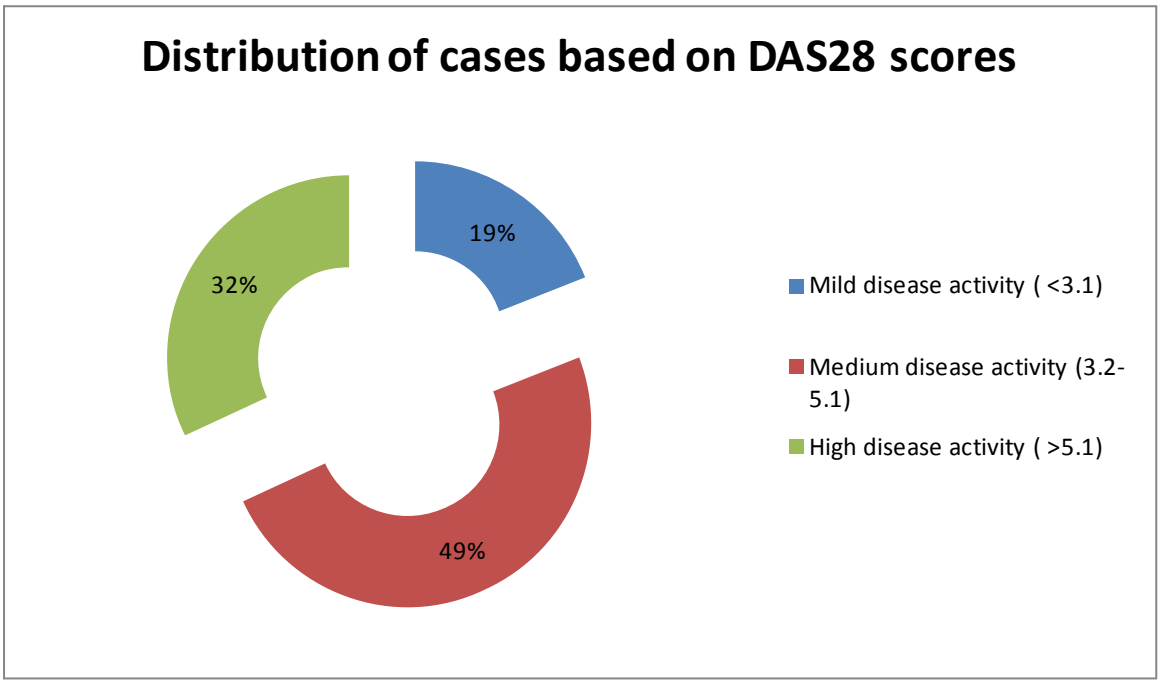


The most common score seen in the patients in the study was 7 followed by 8. The least score seen was 10.

Table 5.3: Distribution of the cases based on DAS28 scores.

DAS28 SCORE	No.of patients
Mild disease activity (<3.1)	19
Medium disease activity (3.2-5.1)	49
High disease activity (>5.1)	32

Chart 5.3: Distribution of the cases based on DAS28 scores.



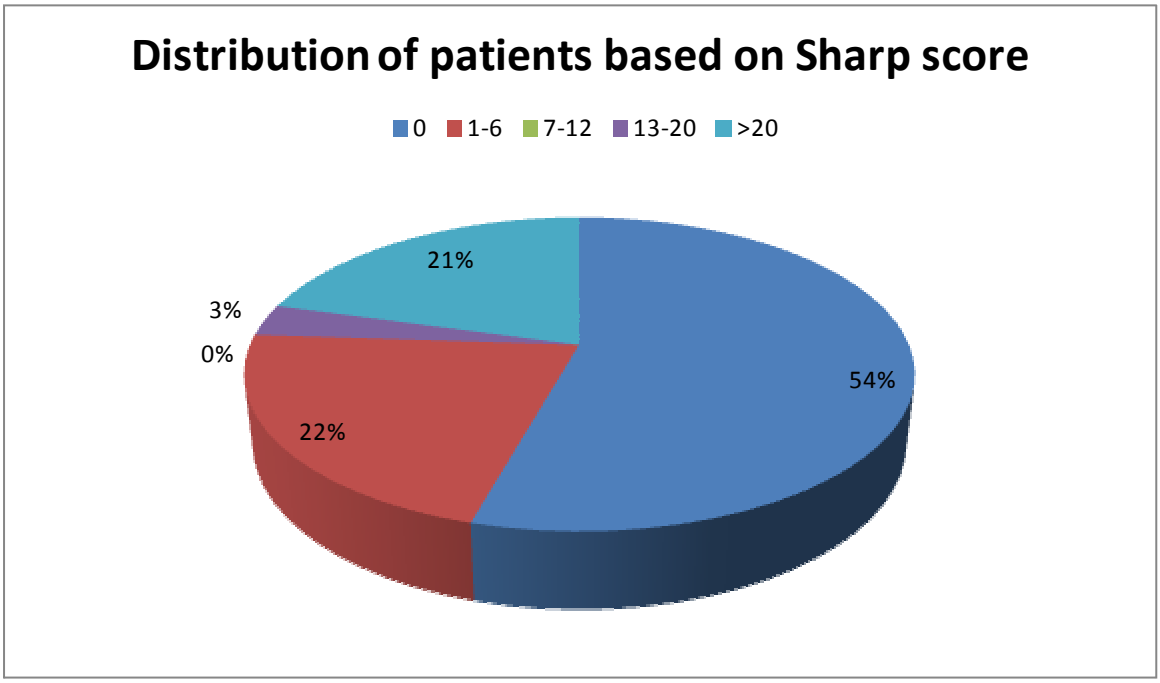
The majority of the cases in the study came under the medium disease activity group (49%). This was followed by the patients in the high disease activity (32%) and then the low disease activity in the group (19%).

Table 5.4: Distribution of Modified Sharp score in the patients of the study

Modified Sharp Score	No. of patients
0	50
1-6	20
7-12	8
13-20	3
>20	19

On examining the radiographs it was found that most common modified Sharp score was 0. This was followed by the range of 1-6 and then > 20.

Chart 5.4a: Distribution of Modified Sharp score in the patients of the study



There are two components of modified Sharp score. One is erosions score and the second one is joint space narrowing.

Chart 5.4b Patients in the study with erosions in X Rays.

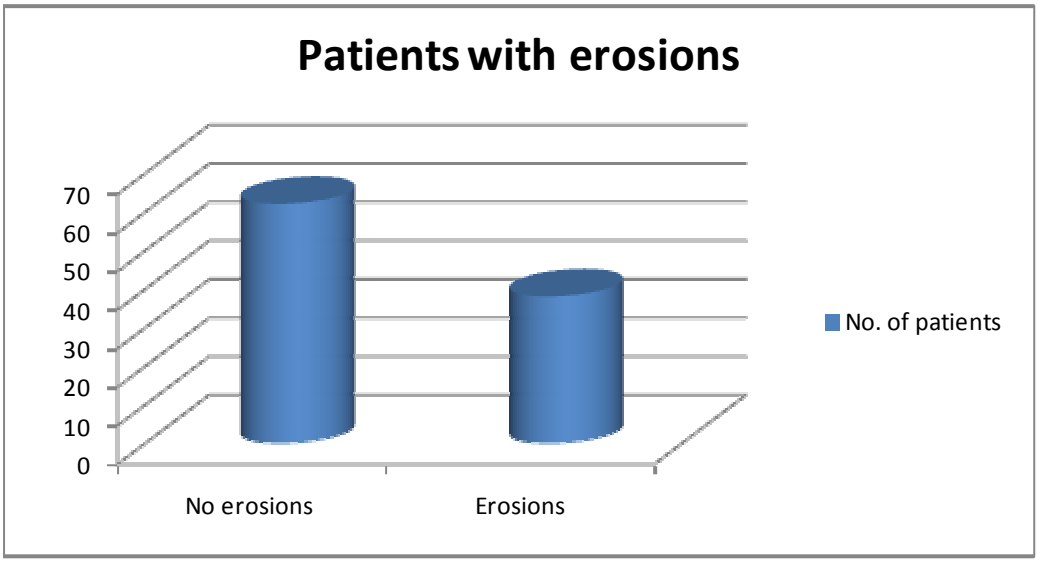
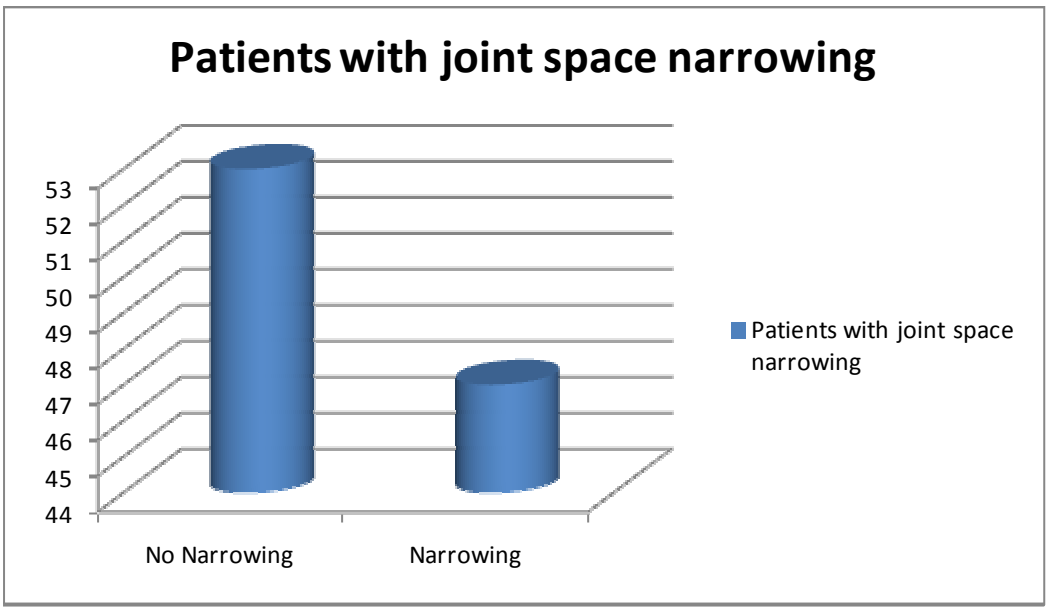


Chart 5.4c Patients with joint space narrowing in X Rays.



38% of our patients had erosions and 47% had joint space narrowing in their X Rays.

Table 5.5 IgM and IgG RF positivity in the patients in the study.

Rheumatoid Factor	POSITIVITY	NEGATIVITY
IgM RF	49	51
IgG RF	31	69

Chart 5.5a IgM RF positivity in the patients in the study.

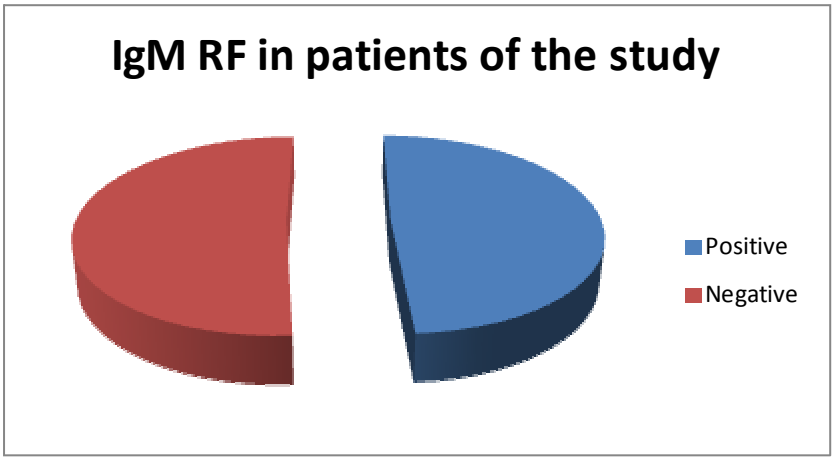
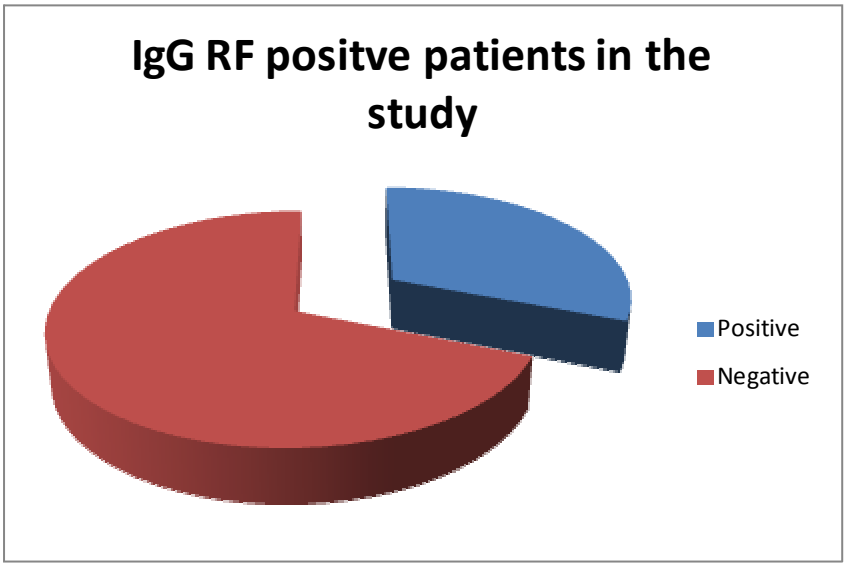


Chart 5.5b IgG RF positivity in the patients in the study.



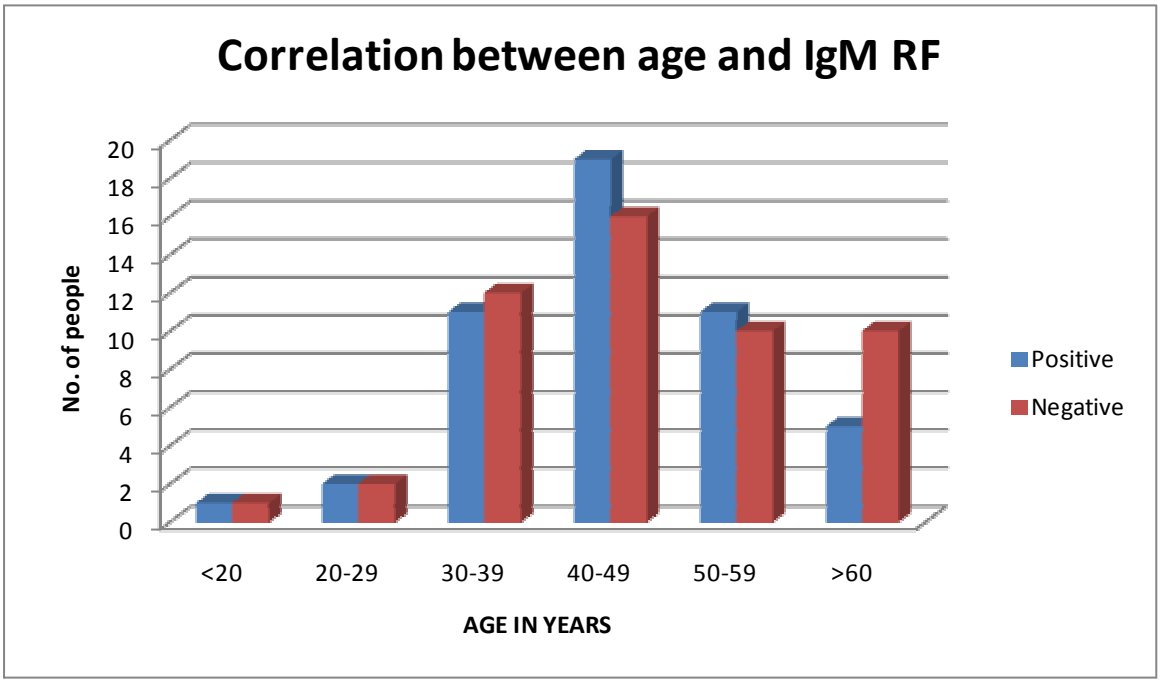
Correlation between various variables

Table:5.6: Correlation of Age distribution with IgM RF

IgM RF	AGE IN YEARS						p= 0.852
	<20	20-29	30-39	40-49	50-59	>60	
Positive	1	2	11	19	11	5	
Negative	1	2	12	16	10	10	

1. In the study, when the age distribution was compared with IgM positivity, it was found out that there was no significant relationship between any age group and IgM positivity. IgM RF tended to be distributed equally in all various age groups. This is illustrated in the chart 5.6

Chart 5.6: Correlation between age and IgM RF

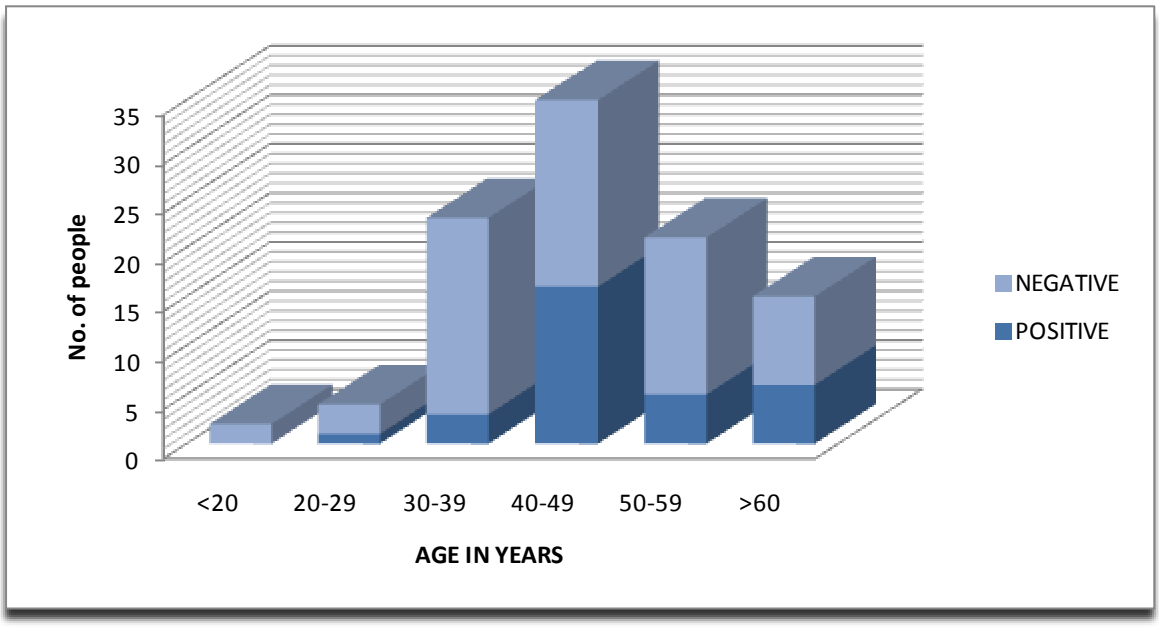


2. Similarly the relationship between various age groups and IgG positivity was also studied as part of the study. The results are put in table 5.7 and chart 5.7.

Table 5.7 : Correlation of age and IgG RF

IgG RF	**AGE IN YEARS**						**p=0.107**
	<20	20-29	30-39	40-49	50-59	60-69	
Positive	0	1	3	16	5	6	
Negative	2	3	20	19	16	9	

Chart 5.7: Correlation between age and IgG RF positivity



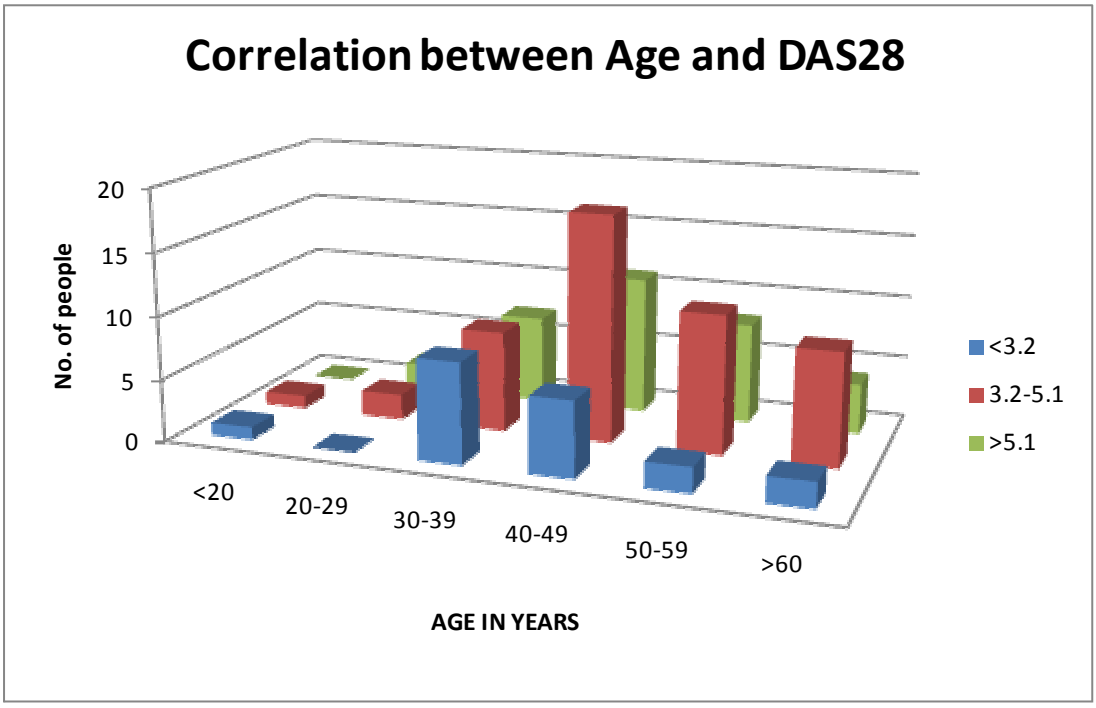
It was found out that IgG positivity also did not have any significant correlation with any specific age group and tended to equally distributed all over the age spectra.

3. The DAS28 scores of various patients were also compared with their respective ages. The results are shown in table 5.8 and chart 5.8.

TABLE 5.8 : Correlation between Age and DAS28

AGE (YEARS)	DAS28 SCORE			p=0.537
	<3.2	3.2-5.1	>5.1	
<20	1	1	0	
20-29	0	2	2	
30-39	8	8	7	
40-49	6	18	11	
50-59	2	11	8	
>60	2	9	4	

Chart 5.8 : correlation between age and DAS28



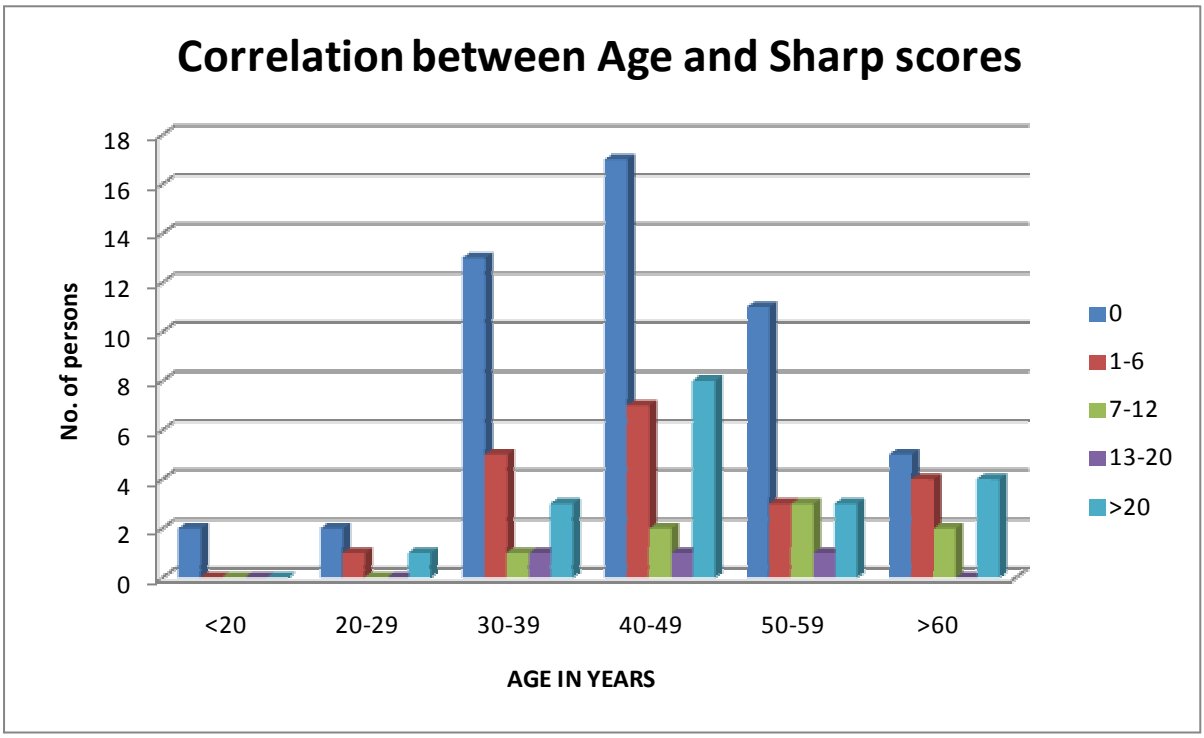
It was found out that the DAS28 scores did not correlate to any specific age group differences and the various scores were distributed along the entire age spectrum.

4. The results of comparison of various modified Sharp scores with the age of the patients are given in table 5.9 and chart 5.9

Table 5.9: Correlation between age (years) and Sharp scores

AGE (YEARS)	Sharp score					p=0.986
	0	1-6	7-12	13-20	>20	
<20	2	0	0	0	0	
20-29	2	1	0	0	1	
30-39	13	5	1	1	3	
40-49	17	7	2	1	8	
50-59	11	3	3	1	3	
>60	5	4	2	0	4	

Chart 5.9 : Correlation between age (years) and Sharp scores



It was found that there was no significant association of modified Sharp score with age distribution- that is patients had erosions and joint space narrowing irrespective of their age.

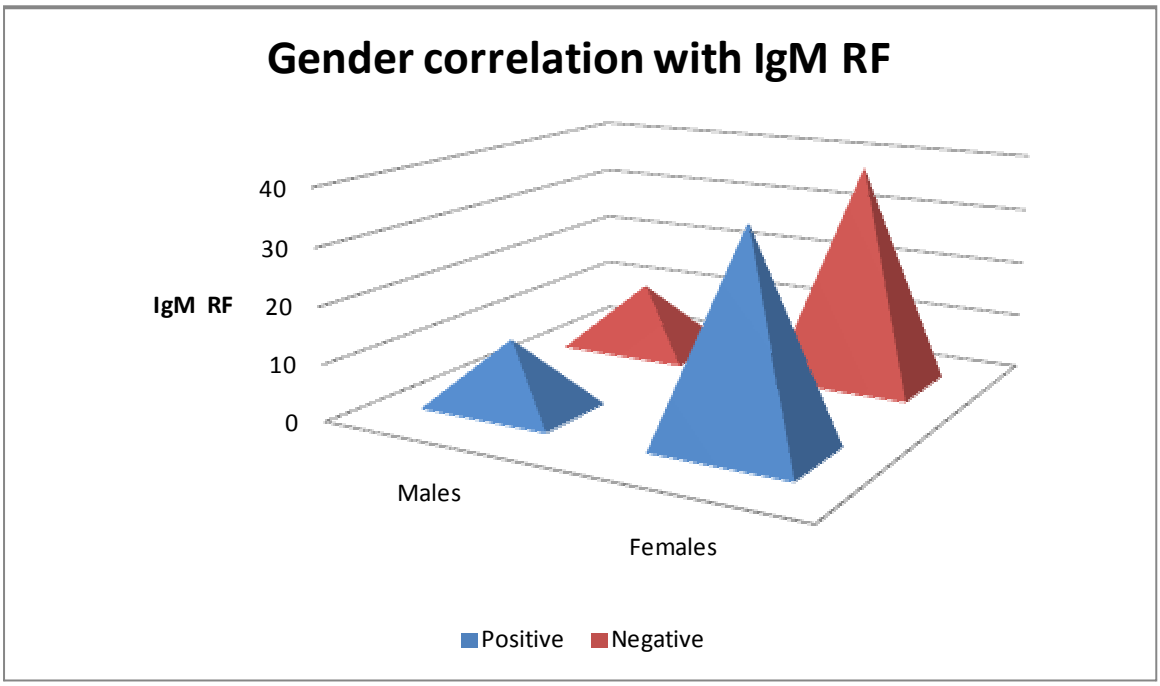
5. Correlation between gender and IgM RF score

The gender of the patients and their IgM RF scores were compared. The results are given in table 5.10 and chart 5.10

Table 5.10 : Correlation between sex distribution and IgM RF

SEX DISTRIBUTION	IgM RF		P=0.548
	Positive	Negative	
Males	12	12	
Females	37	39	

Chart 5.10: Correlation between sex distribution and IgM RF



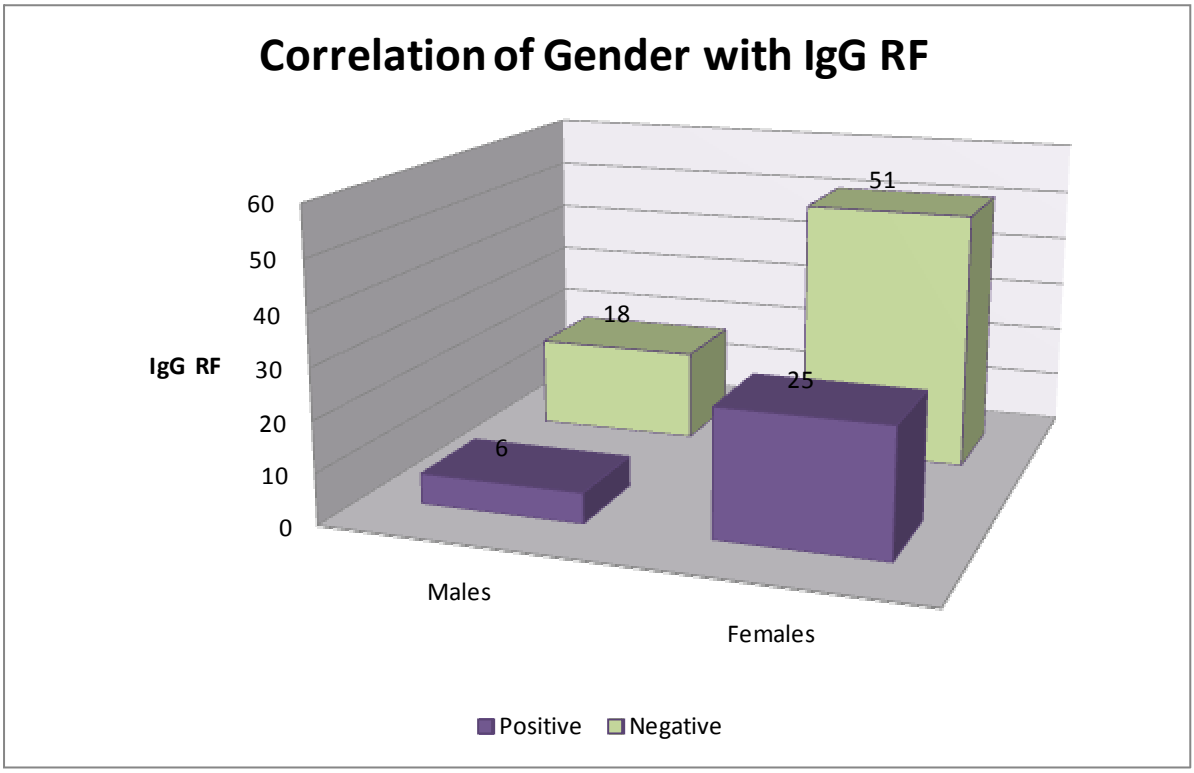
The gender of the patients and their IgM RF positivity and negativity studied. The variables were not found to be significantly associated with a p value of 0.548. So IgM RF occurs in patients irrespective of whether they are males or females.

6. Similar to IgM RF, IgG RF positivity was also studied corresponding to the gender of these patient and its results are given in table 5.11 and chart 5.11.

Table 5.11: Gender correlation with IgG RF

SEX DISTRIBUTION	IgG RF		P<0.322
	POSITIVE	NEGATIVE	
Males	6	18	
Females	25	51	

Chart 5.11: Gender correlation with IgG RF



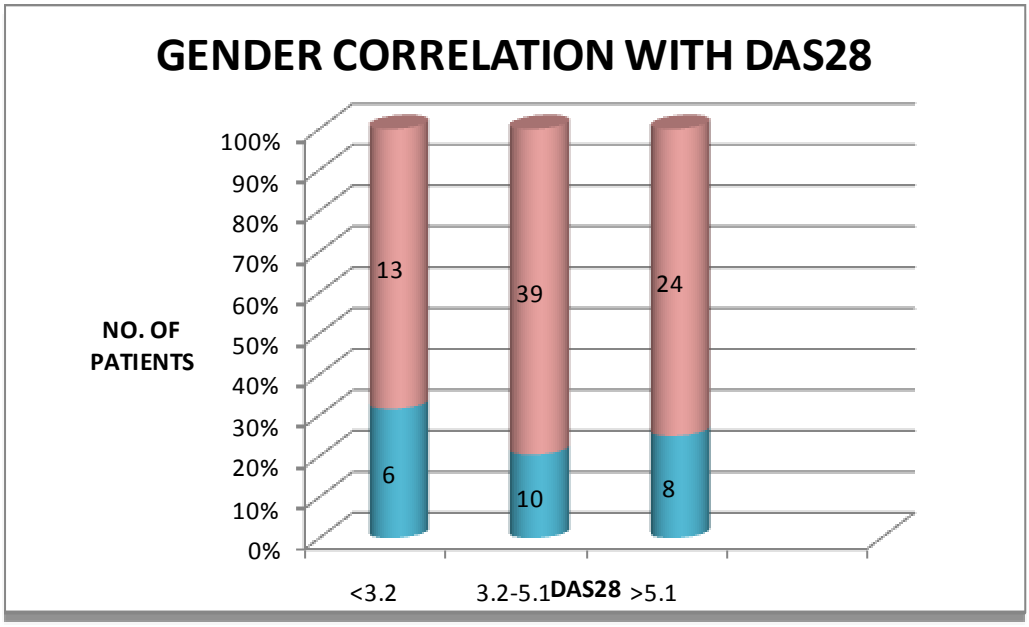
The p value of 0.322 showed that there was no significant association of gender with IgG RF. IgG RF positivity occurred in patients irrespective of them being males or females. Thus it was found that both the antibodies had no significant correlation with the gender of their patients

7. The individual DAS28 scores of all the patients were next studied with the gender of the patients and the result of the study is given in table 5.12 and chart 5.12 that are shown below

Table 5.12: Gender correlation with DAS28

SEX	DAS28			TOTAL	pVALUE
	<3.2	3.2-5.1	>5.1		0.962
Male	6	10	8	24	
Female	13	39	24	76	

Chart 5.12: Gender correlation with DAS28



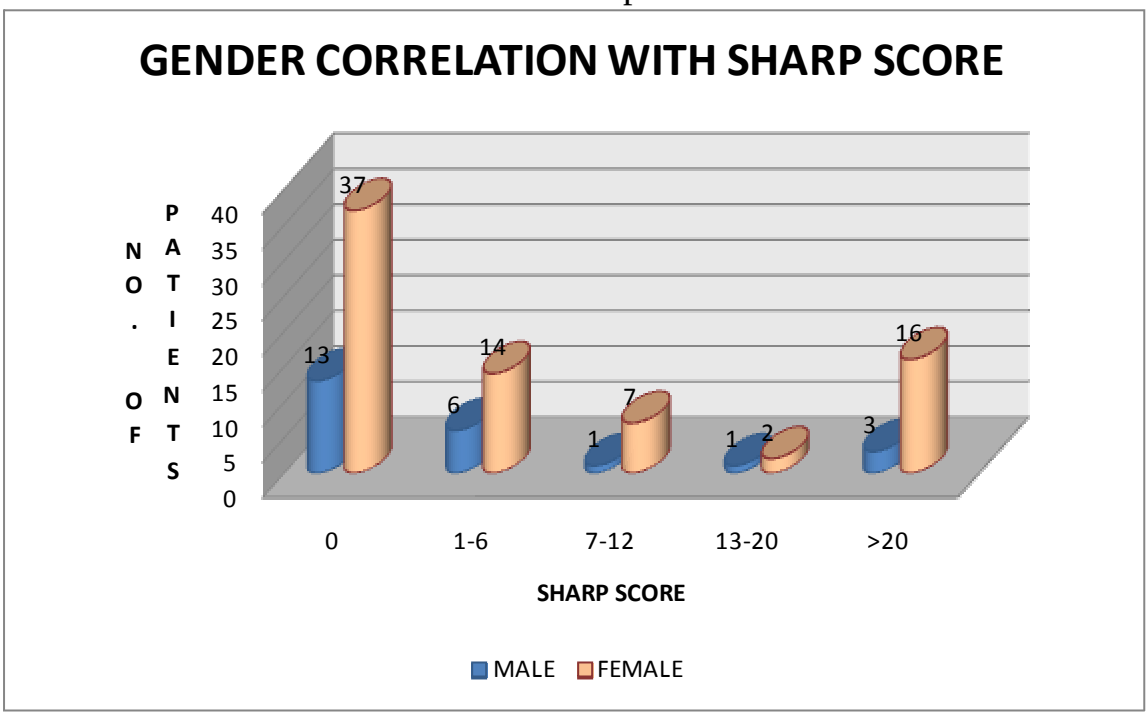
It was found that the DAS28 scores had no significant association with the gender of the patient and was distributed in both males and females.

8. The individual modified Sharp's scores of all the patients were taken and the gender distribution for the various ranges of the score was studied. The results are given in chart 5.13 and table 5.13

Table 5.13 Gender correlation with Sharp score

GENDER	SHARP SCORE					TOTAL	pValue 1.930
	0	1-6	7-12	13-20	>20		
MALE	13	6	1	1	3	24	
FEMALE	37	14	7	2	16	76	

Chart 5.13: Gender correlation with Sharp score



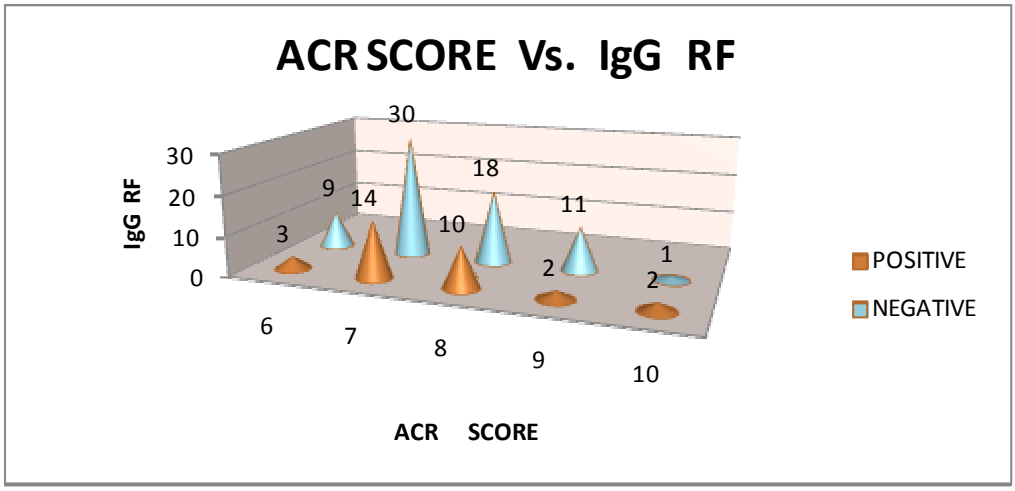
The modified Sharp score did not have any significant correlation to the gender of the patients and erosions and joint space narrowing occurred irrespective of the patient being male or female.

9. The result of the comparison of the ACR score with IgG RF is given in table 5.14 and chart 5.14.

Table 5.14: Correlation of ACR/EULAR score with IgG RF.

ACR	IgG Positive	IgG Negative	
6	3	9	
7	14	30	**P=3.773**
8	10	18	
9	2	11	
10	2	1	

Chart 5.14: Correlation of ACR/EULAR score with IgG RF.



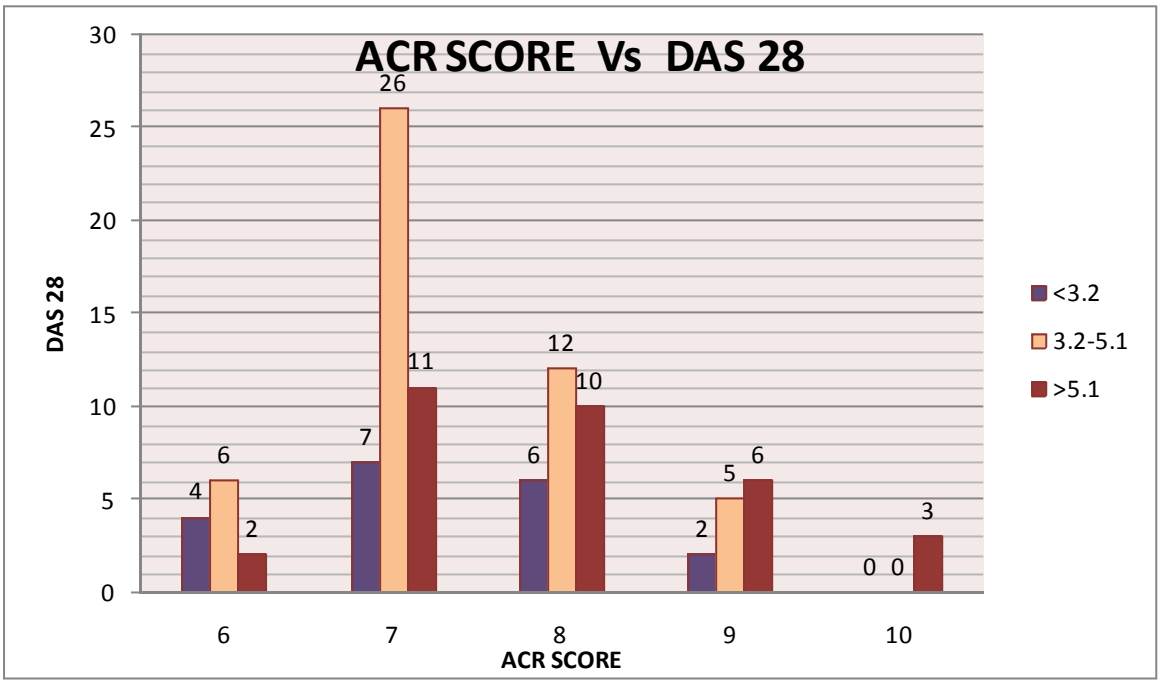
It was found that there was no significant correlation between the two variables. Hence higher ACR score did not indicate increased presence of IgG RF. Comparison with IgM RF was not done as IgM RF was a component of the score.

10. Similarly the ACR/EULAR score was correlated with DAS28 and the results are given in table 5.15 and chart 5.15.

Table 5.15: Correlation between ACR score and DAS28

ACR	<3.2	3.2-5.1	>5.1	Total No.
6	4	6	2	12
7	7	26	11	44
8	6	12	10	28
9	2	5	6	13
10	0	0	3	3

Chart 5.15: Correlation between ACR score and DAS28



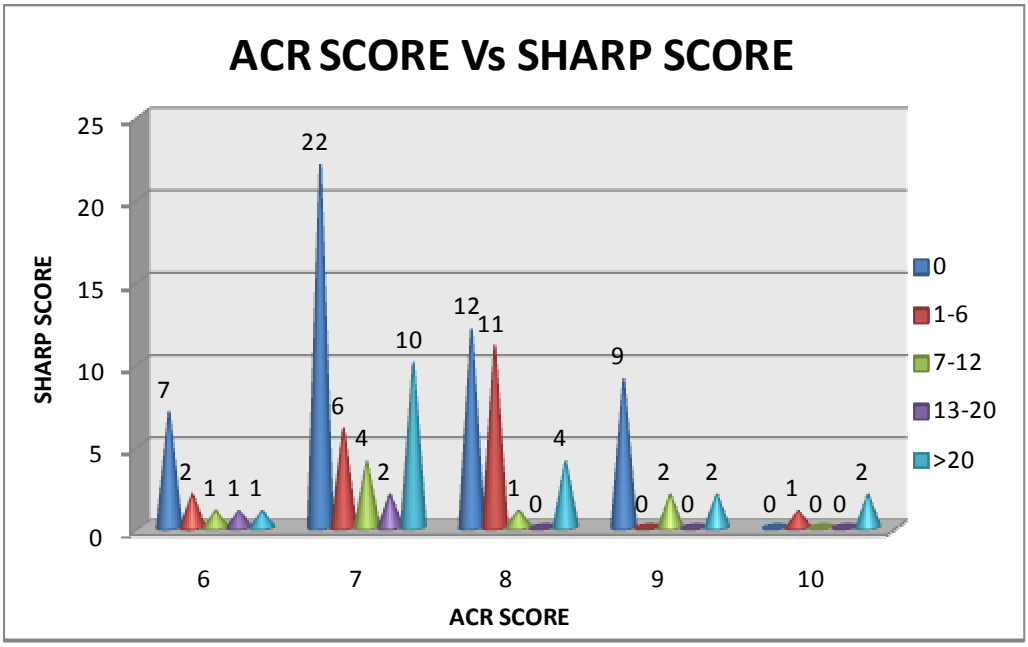
There was no significant correlation between the various ACR scores and DAS28 scores. The higher ACR scores did not correspond to higher DAS28 scores or vice versa.

11. The ACR/EULAR scores was then compared to the modified Sharp's score of the patients and the results are given in table 5.16 and chart 5.16.

Table 5.16: Correlation between ACR score and Sharp score

ACR SCORE	Modified Sharp Score					
	0	**1-6**	**7-12**	**13-20**	**>20**	
6	7	2	1	1	1	**p=0.154**
7	22	6	4	2	10	
8	12	11	1	0	4	
9	9	0	2	0	2	
10	0	1	0	0	2	

Chart 5.16: Correlation between ACR score and Sharp score



There was no significant correlation between the two. The higher ACR/EULAR scores did not correlate to higher modified Sharp scores or vice versa.

12. Correlation between DAS28 and modified Sharp score.

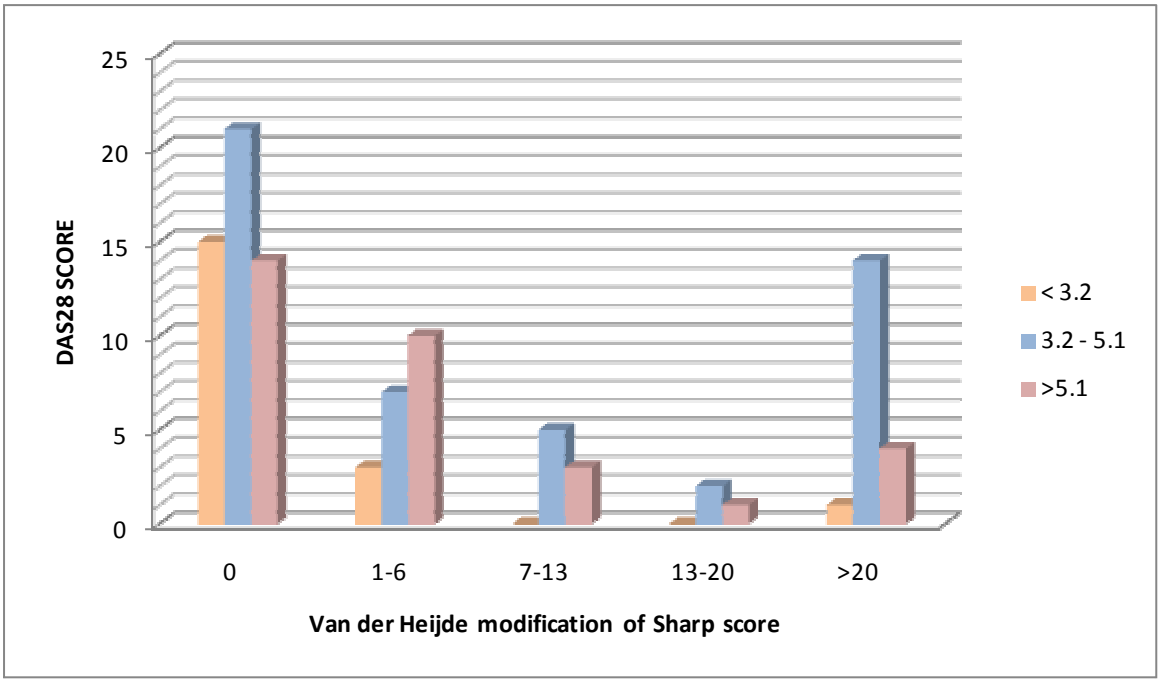
The first part of the study is to study the relationship of the clinical severity scale (DAS28) and compare it with the Van der Heijde modification of Sharp score which gives us the erosions and radiographic severity in the patients. Both the scores were calculated for the 100 patients and recorded. These scores were then compared to determine if the severity tends to correlate in both the scales. The results of the correlation is given in table 5.17 and chapter 5.17

Table 5.17: CORRELATION BETWEEN DAS28 AND SHARP SCORE

SHARP SCORE	DAS28 SCORE			
	<3.2	3.2-5.1	> 5.1	
0	15	21	14	P = 0.069
1-6	3	7	10	
7-13	0	5	3	
13-20	0	2	1	
>20	1	14	4	

The p value of 0.069 shows that though there is an apparent correlation between the two scales there is no statistically significant correlation. The erosions and joint narrowing which categorise worsening of bone changes of a patient tend to occur irrespective of the DAS28 score of the patients

Chart 5.17: CORRELATION BETWEEN DAS28 AND MODIFIED SHARP SCORE



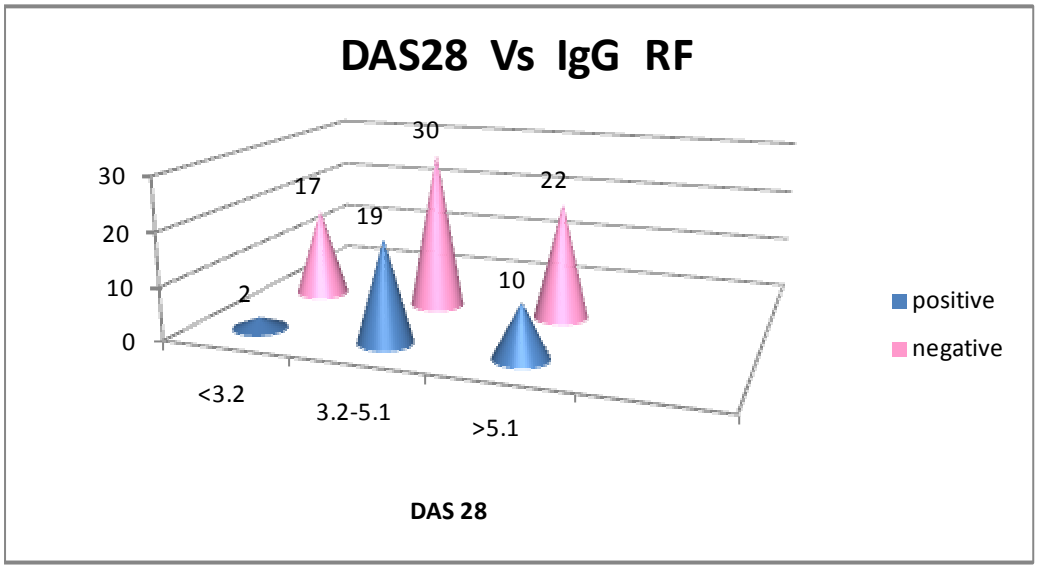
The p value of 0.069 shows that **there is no significant correlation between the DAS28 score and the modified Sharp score of the individual cases.** Patients with an increased radiograph changes did not actually have higher scores in DAS28. Hence though both the scales are commonly used to detect the severity of the disease , it seems that they depict severity in two different parts of the disease. The DAS28 gives an idea of the acute inflammation and synovitis which cripples the patient while the Sharp's score seems to provide us with information of the bone changes which occur in these patients over a period of time and the long term morbidity associated with these changes. Scoring one scale does not help us to predict the scores in the other scale.

13. The DAS28 scores were also compared with IgG RF to determine whether there was any significant correlation and its results are given in table 5.18 and chart 5.18

Table 5.18: Correlation of DAS28 with IgG RF

DAS28 SCORE	IgG RF		
	POSITIVE	NEGATIVE	
<3.2	2	17	P=5.109
3.2-5.1	19	30	
>5.1	10	22	

Chart 5.18: : Correlation of DAS28 with IgG RF



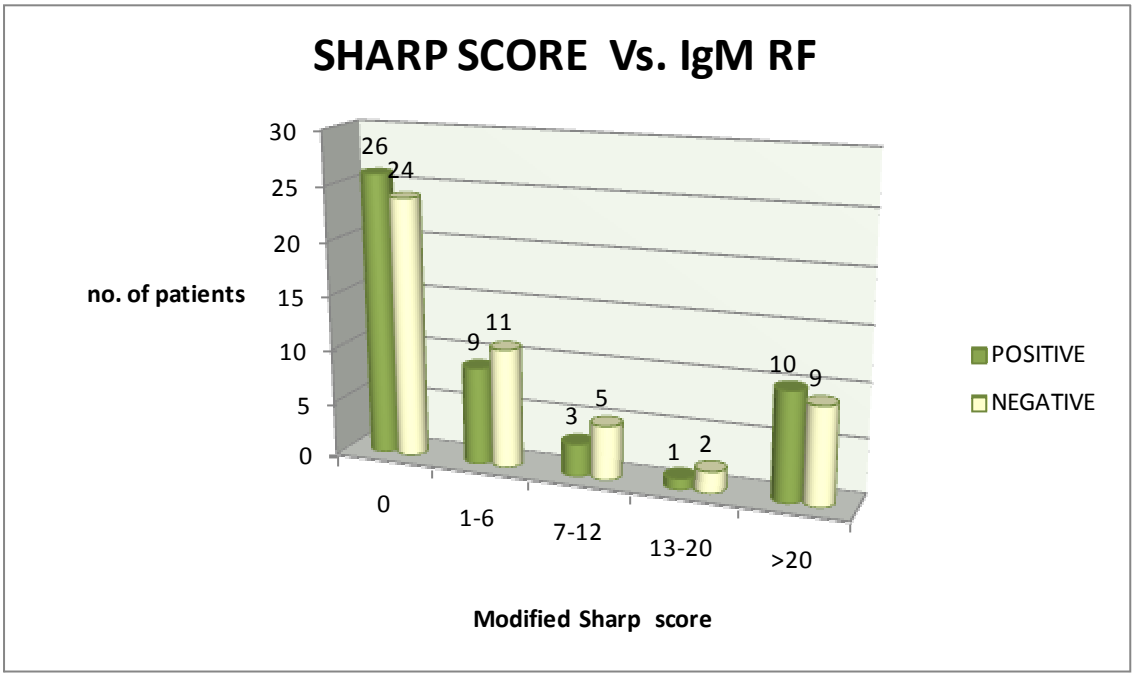
It was found that IgG RF positivity did not correspond to higher severity scores by DAS28. Similarly IgG RF negativity did not correspond to lower scores in DAS28.

14. To determine if bony changes in RA could be predicted by immunological tests the modified Sharp score of the patients were tested with both IgM RF and IgG RF positivity. The result of the correlation between IgM positivity and Sharp score is given in chart 5.19 and table 5.19

Table 5.19: Correlation between Sharp score and IgM RF

SHARP SCORE	IgM RF		TOTAL	
	POSITIVITY	NEGATIVITY		
O	26	24	50	p=1.126
1-6	9	11	20	
7-12	3	5	8	
13-20	1	2	3	
>20	10	9	19	

Chart 5.19: Correlation between Sharp score and IgM RF



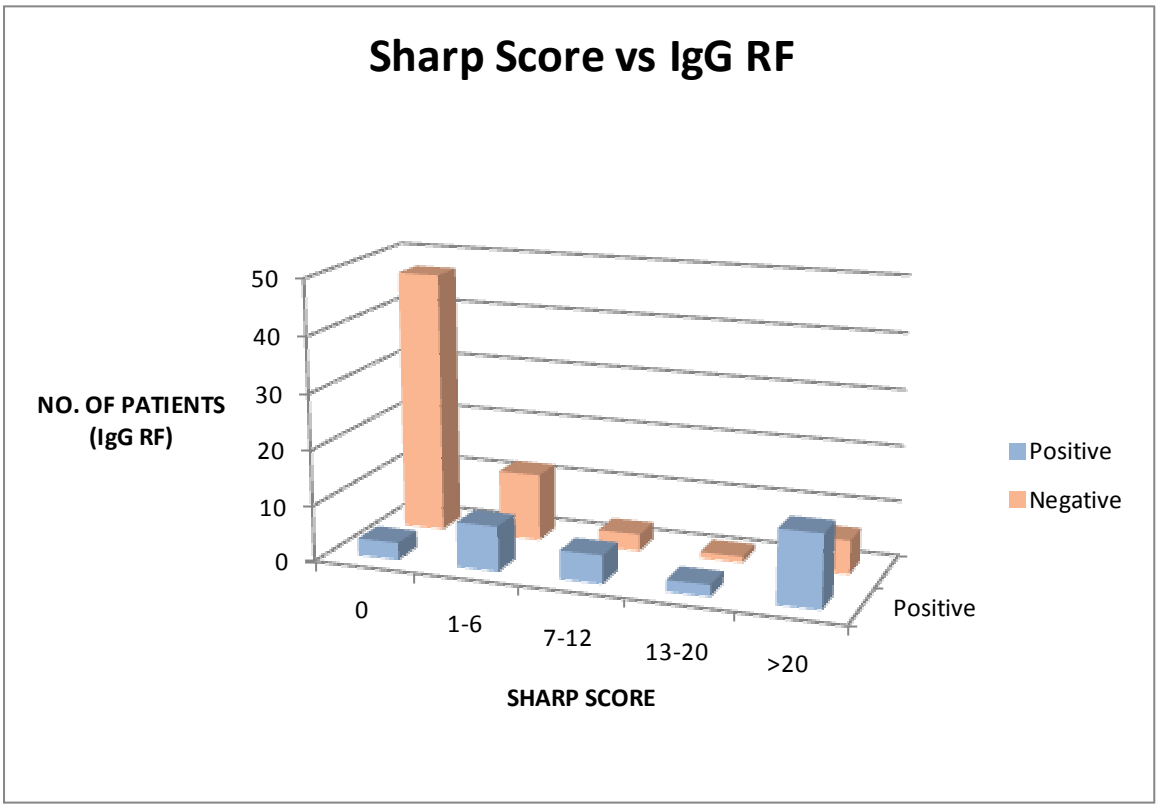
It was found there was no significant correlation of IgM RF with increased erosions and joint space narrowing in radiographs. IgM RF positivity did not correspond to increases bony changes.

15. Similarly IgG RF positivity and the Sharp scores of the various patients of the study were compared. The result of the correlation is given in chart 5.20 and table 5.20.

Table 5.20: Correlation between Sharp score and IgG RF

SHARP SCORE	IgGRF		TOTAL SCORE	
	POSITIVE	NEGATIVE		
0	3	47	50	
1-6	8	12	20	**p < 0.001**
7-12	5	3	8	
13-20	2	1	3	
>20	13	6	19	

Chart 5.20: Correlation between Sharp score and IgG RF



The p value was 0.000 which is noted as less than 0.001. **Hence there was a significant correlation between IgG RF positivity of the patients and the bony changes in the radiographs of these patients. Patients who had IgG RF positivity tend to progress to increased bony changes which are detected by radiographs.**

6. DISCUSSION:

This study was based on the data collected from 100 patients who had been diagnosed as suffering from Rheumatoid arthritis according to the ACR/EULAR CRITERIA FOR RA.[117] The various data collected included age, sex, ACR/EULAR score, IgM RF, IgG RF, DAS28 score and Van der Heijde modification of Sharp score.

The first part of the study was to determine if the 2 types of severity grading – the clinical and the radiological, were comparable.

The **DAS28** scores were calculated for all the patients. **The mean score was 4.54 with a standard deviation of 1.03. The median score value was 4.6 and mode was 3.15.**

Similarly the **Van der Heijde modification of the Sharp score** was calculated for all the individual patients and divided into 5 groups. Because of the present changes only in a part of the people with most others having a score of 0**, the mean was 10.49 with a standard deviation of 22.6.**

It was found that though those patients with **greater Sharp score tended to have higher DAS28 scores it was not significant when determined by statistics.** This showed that **2 scales are not interchangeable**. Similar results are also seen in other studies done in many parts of the world which showed

that the 2 most commonly used methods to detect severity of RA (clinical and radiographs) are actually independent of each other.[7,76,118,119] Hence the latest thought based on various books and studies is that in RA, inflammatory synovitis, represented by the DAS28 and proliferative synovitis which causes erosions and other bony changes and is represented by the modified Sharp score are not the same but actually they reflect two different aspects of the same disease.[8] This is especially important due to the following reasons.

- Most of the various DMARDs are investigated based on their efficacy using one of the 2 scales and hence it is important to realise that DMARDs effective in reducing the acute inflammation and morbidity might not be effective in reducing the progression in bony changes and vice versa.
- Though radiological progression of the disease is very important in preventing long term morbidity, patients with RA generally are more distressed by the acute symptoms like swelling, tenderness and early morning stiffness which are best depicted by clinical scales like DAS28. So though it is important to look for progressions, DAS28 and other clinical scales remain the most important part of management of RA.
- The fact these two scales represent two different pathologies probably means that the clinician should consider treatment against both the pathologies in order to treat the patient comprehensively.

The second part of the study was to determine if the there was any correlation between the DAS28 scores and IgG RF positivity. Out of the 100 patients who were taken for the study IgG RF was positive in 31 of the patients and negative in 69 of the patients. The Sharp score of all the patients were compared. **Our study showed that there was a significant correlation between IgG RF positivity and presence of bony changes seen in radiographs. The p value was less than 0.001(highly significant).**

This assumes importance, especially in the fact that in our study that though IgM RF was positive in many patients with presences of changes in radiographs, there was no significant correlation with a p value more than 0.05. Hence IgG RF can predict radiographical progression and hence can be used as a tool to determine and predict bony changes. This in turn can lead to early detection of patients vulnerable to erosions and other changes and hence more aggressive management in those patients. The finding of the study collaborated with similar studies done around the world which states that though IgM RF is most sensitive and is an important in predicting the clinical severity of the disease other antibodies IgG RF and anti CCP predict bony changes better.[115,120-122]

The results from other data collected from the studies were also studied. The age of the patients in the study varied from 18 to 70 with the mean age being 45.90 years with a standard deviation of 11.29 on both sides. The median age

was 45 years and the maximum patients with a single given age (given by mode) were 35. This age spectrum is similar to that seen in various other studies about RA which says most commonly disease occurs at 35-40 years of age.[18] It was also found that age of the patient did not correspond to different variables that determine the severity of the disease which were studied in the trial.

Among the patients involved in the study the male:female ratio was 1:3 which was similar to that present in other studies. There was no increased presence of disease severity in either of the gender.

There was also no significant correlation between DAS28 and IgG RF, showing that though IgG RF was useful in predicting the radiological progression of the disease, it did not correlate with the clinical severity of the disease.

7. CONCLUSION

- Though both DAS28 and Sharp score both help to determine the severity of the disease, they detect two different aspects of the same disease and are hence not changeable.
- As patients symptoms and present morbidity are best determined by clinical severity scales, DAS28 and other severity scales remain the most important tool to determine the prognosis and plan management.
- Sharp score and other radiological scale do not determine of the severity of the disease but detect bony changes that predict long term morbidity.
- Though IgM RF and anti CCP are most commonly used in RA, IgG RF predicts radiological changes like bony erosions and joint space narrowing and can hence be used to predict long term changes.
- IgG RF positive patients can hence be treated more aggressively in view of their tendency to have bony changes later.
- Newer modalities of investigations like USG and MRI were not taken into consideration.

8. LIMITATIONS OF THE STUDY

1. Study population is small.
2. The study population was consecutively selected. The number of seropositive patients and seronegative patients might not represent their distribution in the general population.
3. Only the most commonly used 2 scales were chosen. Other similar scales were not studied.
4. Long term progression of the disease and its influence on the scales was not studied
5. Similarly the effect of treatment on these scales was not detected as patients who were newly diagnosed alone were included in the study.
6. Anti CCP role to determine the severity of the disease and predicting the radiological changes is not studied and compared with IgG RF.

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ABBREVIATIONS

RA	- Rheumatoid Arthritis
RF	-Rheumatoid Factor
IgG	-Immunoglobulin
EBV	-Ebstein Barr Virus
CMV	-Cytomegalo Virus
HLA	-Human Leucocyte Antigen
IL1	-Interleukin
DAS	-Disease Activity Scale
TNF	-Tumor Necrosis Factor
Anti CCP	-Anti citrullinated protein antibody

PROFORMA

NAME:

AGE:

SEX:

ADDRESS: Rh. No.:

RR. No.:

HISTORY AND PAST HISTORY:

DURATION OF ILLNESS:

SIGNS:

GENERAL

Built:	Pallor:	Icterus:
Pedal oedema:	Fever:	Hydration:
Clubbing	PR:	BP:

CVS:

RS :

PER ABDOMEN:

CNS:

Blood:

Complete haemogram - Hb.

TC

DC

ESR

PLATELETS

Blood – Sugar

Urea

Creatinine

Serum electrolytes Sodium

Potassium

Serum Rheumatoid factor

Serum C-Reactive protein

Urine:

Albumin

Sugar

Deposits.

DAS 28 SCORE

SHARP'S SCORE

IgG RF

JOINT DISTRIBUTION (0-5)	**SCORE**	**PATIENT'S SCORE**
1 large joint	0	
2-10 large joints	1	
1-3 small joints (large joints not counted)	2	
4-10 small joints (large joints not counted)	3	
>10 joints (at least one small joint)	5	
SEROLOGY (0-3)		
Negative RF AND negative ACPA	0	
Low positive RF OR low positive ACPA	2	
High positive RF OR high positive ACPA	3	
SYMPTOM DURATION (0-1)		
<6 weeks	0	
≥6 weeks	1	
ACUTE PHASE REACTANTS (0-1)		
Normal CRP AND normal ESR	0	
Abnormal CRP OR abnormal ESR	1	
TOTAL SCORE		

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE, CHENNAI-10

Ref.No.161/ME-1/Ethics/2013 Dt:07.02.2013.

CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study of Correlation of disease severity by clinical assessment, Radiological assessment and IgG rheumatoid factor in patients with rheumatoid arthritis " for Project work submitted by Dr. V. Madhav, MD (General Medicine) II nd year PG Student, Kilpauk Medical College, Chennai.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

12/2/13.

CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,Chennai

GOVT. KILPAUK MEDICAL COLLEGE
12 FEB 2013
Kilpauk, Chennai-10.

11/2

MASTER CHART

NAME	AGE	SEX	OP No.	ACR SCORE	IgM RF	DURATION	ESR	Tender Jts	Swollen Jts	DAS 28	Xray erosion	Jt. Narr	Total Score	IgG RF
NARMADHA	40	F	763/12	10	POS	3 YEARS	50	22	27	7.94	100	59	159	POSITIVE
KARPAGAM	56	F	298/12	8	NEG	1 YEAR	24	12	7	5.76	1	8	9	POSITIVE
RAMAYEE	45	F	303/11	10	POS	2 YEARS	30	13	3	5.44	27	21	48	POSITIVE
RAMESH	38	M	403/11	10	POS	5 YEARS	27	20	8	6.72	0	4	4	NEGATIVE
RUKMANI	56	F	520/11	7	NEG	9 MONTHS	25	5	1	4.35	6	4	10	NEGATIVE
KASIYAMMAL	50	F	101/12	7	NEG	2 YEARS	40	8	1	5.15	0	0	0	NEGATIVE
DEVI	30	F	97/12	8	NEG	8 MONTHS	20	2	0	3.17	3	0	3	NEGATIVE
KUMARI	45	F	790/11	9	POS	8 MONTHS	20	8	2	4.5	0	0	0	NEGATIVE
SUGUNA	40	F	521/12	7	NEG	5 MONTHS	80	4	0	4.61	0	0	0	NEGATIVE
KANNAGA	48	F	86/11	8	POS	1 YEAR	82	8	2	5.62	0	3	3	POSITIVE
ANUSHYA	49	F	55/12	7	NEG	3 YEARS	25	2	0	3.05	0	1	1	NEGATIVE
MANICKAM	40	M	660/11	7	NEG	1 YEAR	60	4	3	5.03	20	17	37	POSITIVE
LAKSHMI	53	F	528/11	7	POS	7 MONTHS	70	4	2	4.91	0	0	0	NEGATIVE
SELVI	43	F	49/11	8	POS	2 YEARS	30	4	1	4.76	16	8	24	POSITIVE
VISALATCHI	48	F	321/12	7	NEG	2 YEARS	42	11	2	5.29	2	8	10	POSITIVE
VASANTH	47	M	32/12	8	POS	1 YEAR	15	2	0	2.97	0	4	4	POSITIVE
DEVA	38	M	34/11	7	NEG	2 YEARS	10	4	0	3.01	0	0	0	NEGATIVE
VANITHA	44	F	50/12	7	NEG	1 YEAR	15	4	2	3.58	1	1	2	POSITIVE
JAYARANI	55	F	35/11	7	POS	3 YEARS	10	5	2	3.82	17	12	29	POSITIVE
MEERA	42	F	167/12	8	POS	6 MONTHS	62	5	3	5.05	0	0	0	NEGATIVE
RAJAMANI	63	M	358/11	6	NEG	18 MONTHS	15	1	1	3.16	0	0	0	NEGATIVE
MEENATCHI	35	F	39/10	7	NEG	2 YEARS	15	8	0	3.76	0	0	0	NEGATIVE

RAGHUPATHI	42	M	113/12	7	NEG	2 YEARS	20	8	3	4.73	32	18	50	POSITIVE
LATHA	45	F	302/11	8	POS	1 YEAR	95	17	8	6.99	10	20	30	POSITIVE
MOHAN	50	M	303/12	7	POS	15 MONTHS	20	12	7	5.48	2	1	3	NEGATIVE
KALAVATHY	62	F	352/12	8	NEG	5 YEARS	90	6	1	5.36	2	0	4	NEGATIVE
THABITHAL	36	F	213/12	7	NEG	6 MONTHS	132	13	7	6.74	0	1	1	NEGATIVE
MEENATCHI	70	F	88/11	7	NEG	30 MONTHS	93	1	1	4.57	14	8	22	NEGATIVE
MOHANDASS	18	M	45/13	7	POS	4 MONTHS	12	12	4	4.8	0	0	0	NEGATIVE
THAYALNAYAGI	45	F	741/12	8	POS	1 YEAR	50	10	8	5.19	0	0	0	NEGATIVE
GEETHALAKSHMI	26	F	98/12	8	POS	10 MONTHS	32	8	2	4.69	0	0	0	NEGATIVE
NAGAMMAL	60	F	235/11	8	POS	1 YEAR	36	3	1	4.18	0	3	3	POSITIVE
NISHA	30	F	211/12	6	NEG	1 YEAR	4	8	2	3.09	0	0	0	NEGATIVE
LALITHA	70	F	70/13	7	NEG	6 MONTHS	75	16	8	6.61	0	0	0	POSITIVE
SHANMUGHAVALLI	43	F	95/11	9	POS	4 YEARS	10	3	0	3	0	0	0	NEGATIVE
SUSEELA	38	F	673/12	8	POS	2 YEARS	20	4	0	4.2	24	18	42	POSITIVE
KALAISELVI	46	F	360/12	6	NEG	1 YEAR	22	4	2	4.24	8	3	11	POSITIVE
VINAYAGAM	30	M	53/12	6	NEG	2 YEARS	126	0	0	3.67	4	2	6	POSITIVE
VIJAYA	38	F	110/13	8	POS	2 YEARS	40	6	2	4.91	0	0	0	NEGATIVE
VIMALA	57	F	541/12	6	NEG	3 YEARS	37	3	0	3.92	0	0	0	NEGATIVE
INDRA	56	F	594/12	7	POS	4 MONTHS	40	4	0	4.26	6	8	14	POSITIVE
KRISHNAVENI	65	F	601/12	7	NEG	1 YEAR	22	4	1	4.12	0	0	0	NEGATIVE
CHANDRA	58	F	628/11	7	NEG	1 YEAR	54	2	0	4.14	2	2	4	POSITIVE
RAJALAKSMI	53	F	163/11	8	POS	8 YEARS	52	3	2	4.83	42	48	90	POSITIVE
USHNARA	43	F	152/11	6	NEG	2 YEARS	100	7	3	5.89	0	0	0	NEGATIVE
SALMA BEEVI	52	F	75/13	6	NEG	2 YEARS	20	10	5	5.19	0	4	4	NEGATIVE
SANTHOSH KUMAR	18	M	77/13	6	NEG	3 YEARS	12	3	1	3.13	0	0	0	NEGATIVE
TAMARAI SELVI	35	F	200/12	7	NEG	1 YEAR	14	2	2	3.18	0	0	0	NEGATIVE

VAIJAYANTHI	54	F	313/12	7	POS	2 YEARS	73	5	2	5.21	0	0	0	NEGATIVE
RAJA	40	M	719/12	8	POS	5 MONTHS	67	6	4	5.43	1	0	1	NEGATIVE
BHUVANESHWARI	35	F	128/12	7	POS	2 YEARS	65	2	0	4.13	0	0	0	NEGATIVE
KANI	55	F	381/12	8	POS	6 YEARS	6	3	2	3.04	0	0	0	NEGATIVE
GUNASUNDARI	44	F	476/11	7	NEG	3 YEARS	16	2	0	3.15	0	0	0	NEGATIVE
SENGUDI	43	F	314/11	8	POS	2 YEARS	12	2	0	2.95	0	0	0	NEGATIVE
SELVI	42	F	207/11	7	NEG	3 YEARS	42	4	0	4.16	2	1	3	POSITIVE
KANAGI	60	F	222/11	7	NEG	3 YEARS	20	3	1	3.77	12	10	22	NEGATIVE
KUPPAMMAL	60	F	390/11	7	NEG	4 YEARS	46	5	2	4.75	2	8	10	POSITIVE
ALLI	43	F	295/11	7	NEG	1 YEAR	75	6	2	5.21	0	0	0	NEGATIVE
VIJAYA	47	F	363/12	7	POS	8 MONTHS	38	4	3	4.57	4	20	24	POSITIVE
SATHYA	35	F	55/12	8	POS	2 YEARS	10	4	0	3.15	0	0	0	NEGATIVE
PANCHALAI	36	F	363/12	6	NEG	8 MONTHS	40	5	3	4.74	5	16	21	NEGATIVE
SUNDAR	50	M	310/11	7	POS	2 MONTHS	44	4	1	4.47	0	0	0	NEGATIVE
MARY	36	F	271/11	7	NEG	10 YEARS	13	2	1	3.15	16	42	58	NEGATIVE
CHANDRAN	54	M	180/12	7	POS	1 YEAR	44	7	1	4.69	0	7	7	NEGATIVE
LAKSHMI	70	F	89/13	7	NEG	2 YEARS	36	5	3	4.53	34	32	66	POSITIVE
DEIVASIGNAMANI	38	M	53/11	7	NEG	1 YEAR	20	2	0	3.17	0	0	0	NEGATIVE
MUMTAJ	30	F	113/12	9	POS	1 YEAR	105	4	3	5.14	0	0	0	NEGATIVE
REKHA	29	F	251/12	8	POS	18 MONTHS	24	8	8	5.16	0	2	2	NEGATIVE
CHITRA	52	M	28/13	7	NEG	6 MONTHS	22	2	0	3.1	0	0	0	NEGATIVE
MUTHU	27	M	293/11	7	NEG	3 MONTHS	86	12	3	5.96	36	28	64	POSITIVE
RAJESHWARI	45	F	298/11	6	NEG	3 YEARS	14	1	1	3.11	0	0	0	POSITIVE
INDUMATHY	37	F	137/13	6	NEG	3 MONTHS	79	2	2	4.67	0	0	0	NEGATIVE
LAKSHMI	54	F	138/13	8	POS	4 MONTHS	59	8	6	5.54	0	0	0	NEGATIVE
BABY	50	F	101/10	7	NEG	10 YEARS	34	5	1	4.42	0	0	0	NEGATIVE
ROSE	68	F	483/12	8	NEG	10 YEARS	18	3	0	3.41	0	2	2	NEGATIVE
SAROJA	40	F	171/10	7	NEG	3 YEARS	20	3	2	3.88	0	0	0	NEGATIVE

SUGUNAMMA	46	F	140/13	8	POS	1 YEAR	22	6	2	4.35	0	0	0	POSITIVE
RAJESH	27	M	464/11	8	NEG	6 YEARS	30	4	0	3.92	0	0	0	NEGATIVE
THALAIKANI	32	M	57/13	9	POS	18 MONTHS	22	2	0	3.38	0	0	0	NEGATIVE
GEETHA	46	F	126/13	6	NEG	8 MONTHS	40	3	4	4.53	2	16	18	NEGATIVE
SUSILA	60	F	207/11	9	POS	2 YEARS	40	4	0	4.12	0	8	8	POSITIVE
RATHINAPY	46	F	317/12	8	POS	5 MONTHS	100	2	0	4.4	2	2	4	NEGATIVE
AMEENA	35	F	231/11	9	POS	3 YEARS	20	1	0	3.08	0	0	0	NEGATIVE
SHAKILA	34	F	186/13	9	POS	2 YEARS	42	8	3	5.11	5	3	8	NEGATIVE
KASIYAMMAL	50	F	611/12	7	NEG	4 YEARS	40	4	2	5.22	0	0	0	NEGATIVE
SAMUNDESHWARAN	35	M	189/13	8	POS	6 MONTHS	20	7	5	5.18	0	2	2	NEGATIVE
SUBHATRA	65	F	179/10	9	POS	2 YEARS	110	4	0	5.11	0	0	0	NEGATIVE
GANGA BHARANI	65	F	174/12	9	POS	4 YEARS	50	4	2	4.95	10	12	22	NEGATIVE
JAVED	38	M	111/12	7	NEG	3 MONTHS	60	14	4	6.08	8	8	16	POSITIVE
THANGAPILLAI	55	M	228/13	9	POS	1 YEAR	55	10	6	5.82	0	0	0	NEGATIVE
RAMANI	47	M	116/12	8	POS	8 MONTHS	20	8	3	4.73	0	0	0	NEGATIVE
MEENAKUMARI	49	F	196/13	7	NEG	5 YEARS	20	9	3	4.82	0	0	0	NEGATIVE
SUBATRA	61	F	215/13	8	POS	3 YEARS	16	0	0	2.5	0	0	0	NEGATIVE
PANTHANAM	55	F	439/12	7	NEG	3 YEARS	25	6	4	4.59	4	20	24	NEGATIVE
MAHESH	48	M	296/11	7	NEG	1 YEAR	42	6	3	5	0	0	0	NEGATIVE
ASPUGI	60	F	237/13	8	NEG	3 MONTHS	22	9	6	5.23	1	1	2	POSITIVE
ANU	37	F	323/11	9	POS	1 YEAR	125	3	1	5.33	0	0	0	NEGATIVE
POONGAVANAM	42	F	321/12	9	POS	2 YEARS	64	9	4	5.85	0	0	0	NEGATIVE
VELLAISAMY	47	M	171/13	7	POS	2 YEARS	42	4	4	5.28	0	0	0	NEGATIVE
BANU	45	F	208/13	9	POS	3 YEARS	39	3	2	4.49	14	24	38	POSITIVE